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— COMMITTED TO PROTECTION OF THE ENVIRONMENT —

FINAL HUMAN HEALTH EXPOSURE ASSESSMENT FOR ROCKY MOUNTAIN ARSENAL VOLUME II-A TOXICITY ASSESSMENT

VERSION 4.1
SEPTEMBER 1990
CONTRACT NO. DAAA15-88-D-0024
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EBASCO SERVICES INCORPORATED
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13. ABSTRACT *(Maximum 200 words)*

THE OBJECTIVES OF THE HUMAN HEALTH EXPOSURE ASSESSMENT INCLUDE:

1. ESTIMATE THE TYPE AND MAGNITUDE OF EXPOSURES TO CONTAMINANTS
2. IDENTIFY CONTAMINANTS OF CONCERN
3. IDENTIFY SITES FOR REMEDIAL ACTION
4. RECOMMEND SITES FOR THE NO ACTION REMEDIAL ALTERNATIVE
5. PROVIDE A BASIS FOR DETAILED CHARACTERIZATION OF THE RISK ASSOCIATED WITH ALL SITES.

THIS DOCUMENT CONSISTS OF THE FOLLOWING: AN EXCUTIVE SUMMARY. VOL.I - LAND USE AND EXPOSED POPULATION EVALUATIONS. VOL.II & III - TOXICITY ASSESSMENT (INCLUDES ARMY AND SHELL TOXICITY PROFILES). VOL. IV - PPLV METHODOLOGY. VOL. V - PPLV CALCULATIONS. VOL. VI - STUDY AREA EXPOSURE ANALYSIS (A INTRODUCTION, B WESTERN STUDY AREA, C SOUTHERN STUDY AREA, D NORTHERN CENTRAL STUDY AREA, E CENTRAL STUDY AREA, F EASTERN STUDY AREA, G SOUTH PLANTS STUDY AREA, AND H NORTH PLANTS STUDY AREA. VOL. VII - SUMMARY EXPOSURE ASSESSMENT. VOL. VIII -

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FINAL
HUMAN HEALTH EXPOSURE ASSESSMENT FOR ROCKY MOUNTAIN ARSENAL
VOLUME II-A
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U.S. ARMY PROGRAM MANAGER'S OFFICE
FOR THE ROCKY MOUNTAIN ARSENAL CONTAMINATION CLEANUP

Prepared by Shell Oil Company

DISCLAIMER STATEMENT

The toxicity profiles contained in Volume II-A and Volume III-A were provided by Shell Oil Company. They are intended to provide additional toxicity information for certain chemicals. The numerical estimates of toxicity used in the PPLVs computed in the Human Health Exposure Assessment for Rocky Mountain Arsenal are those contained in the toxicity profiles prepared by the Army in Volume II and Volume III.

Prepared by Shell Oil Company

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ALDRIN/DIELDRIN

SUMMARY

The cyclodiene pesticides aldrin and dieldrin are no longer manufactured or used in the U.S. (HSDB, 1990). In the environment, aldrin readily degrades to its persistent epoxide derivative dieldrin. Both are acutely toxic, with LD_{50} values ranging from 39 to 60 mg/kg in rats. They have been associated with large-scale kills of terrestrial wildlife in treated areas, and are also very toxic to aquatic organisms. Both pesticides are hepatocarcinogenic in mice, but no treatment-related tumors, in liver or other tissues, have been observed in any other species exposed to aldrin/dieldrin. Other indices of effects on the liver have been reported in dogs (hypertrophy) and monkeys (enzyme induction), but not in humans. Aldrin and dieldrin may cause embryotoxicity, but are apparently not teratogenic. Reproductive toxicity has been reported in animals, but only at high dose levels which also caused parental toxicity. Aldrin and dieldrin may cause central nervous system abnormalities following chronic exposure. Neither compound is considered to be genotoxic/mutagenic in a wide variety of *in vitro* and *in vivo* assays.

CHEMICAL AND PHYSICAL PROPERTIES

CAS Number: Aldrin: 309-00-2
Dieldrin: 60-57-1

Chemical Formula: Aldrin: $C_{12}H_8Cl$
Dieldrin: $C_{12}H_8Cl_6O$

IUPAC Name:

Aldrin: 1,2,3,4,10,10-hexachloro-1,4,4a,5,8, 8a-hexahydro-1,4:5,8-exo-dimethanonaphthalene.

Dieldrin: 1,2,3,4,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-endo-,exo-1,4:5,8-dimethoanonaphthalene.

Molecular Weights: Aldrin: 365
Dieldrin: 381

Melting Point: Aldrin: 104 C
Dieldrin: 176 C

Solubility in Water: Aldrin: 27 ug/liter at 27 C
Dieldrin: 186 ug/liter at 20 C

Solubility in Organics: Soluble in most organic solvents

Log Octanol/Water Partition Coefficient (K_{ow}):

Aldrin: 5.66 (Geyer *et al.*, 1984)
7.40 (Briggs, 1981)
5.66 (Kenaga, 1980) Table III
5.30 (U.S. EPA, 1986)

Dieldrin: 4.32 (Davies and Dobbs, 1984)
6.2 (Briggs, 1981)
3.69 (Rao and Davidson, 1983)
5.48 (Kenaga, 1980) Table III
3.5 (U.S. EPA, 1986)

Soil/Water Partition Coefficient (K_{ow}):

Aldrin:

76,000	Versar (1984)
28,200	Briggs (1981)
96,000	U.S. EPA (1986)

Dieldrin:

3,300; 12880	Kadeg *et al.* (1986) Literature Values
7,413	Briggs (1981)
35,600	Kenaga (1980)

Bioconcentration Factor

Aldrin

1,555	Davies and Dobbs (1984) Eqn C (log k_{ow} = 5.66)
13,640	Davies and Dobbs (1984) Eqn C (log k_{ow} = 7.4)
1,500	Lyman *et al.* (1982)
3,140	Kenaga (1980)
10,800	Kenaga (1980)
3,690	Davies and Dobbs (1984) Eqn B (log k_{ow} = 5.66)
40,345	Davies and Dobbs (1984) Eqn C (log k_{ow} = 7.4)
11 ,792	Lyman *et al.* (1982) Eqn 5-2 (log k_{ow} = 5.66)
247,742	Lyman *et al.* (1982) Eqn 5-2 (log k_{ow} 7.4)
1,810	Davies and Dobbs (1984) Eqn C (log k_{ow} 6.12)
6,940	Davies and Dobbs (1984) Eqn B (log k_{ow} 6.12)
26,400	Lyman *et al.* (1982) Eqn 5-2 (log k_{ow} = 6.12)

Dieldrin

5,800, 4,420	Kenaga (1980) Table 3 (experimental)
1,489	Davies and Dobbs (1984) Eqn B (log k_{ow} = 5.0)

12,590	Davies and Dobbs (1984) Table 2 (experimental)
292	Davies and Dobbs (1984) Eqn C (log k_{ow} = 4.32)
1,130	Lyman *et al.* (1982) Eqn 5-2 (log k_{ow} = 4.32)
30,339	Lyman *et al.* (1982) Eqn 5-2 (log k_{ow} 6.2)
480	Davies and Dobbs (1984) Eqn A (S = 0.25)
3,700	Lyman *et al.* (1982) Eqn (log k_{ow} = 5.0)

Vapor Pressure: Aldrin: 2.31 x 10-5mm Hg at 20 C
Aldrin: 6 x 10-6mm Hg (U.S. EPA 1986)
Dieldrin: 2.8 x 10-8mm Hg at 250 C

Henry's Law Constant:

Aldrin: 2.4 x 10-5 atm=m3/mole (calculated)
1.6 x 10^{-5} atm-m^3/mole (U.S. EPA 1986)

Dieldrin: 1.4 x 10^{-5} atm-m^3/mole (calculated)
4.58 x 10^{-7} atm-m^3/mole (U.S. EPA)

ENVIRONMENTAL TRANSPORT AND FATE

The range of experimental and estimated soil-water partition coefficients reported above indicates that substantial sorption of aldrin and dieldrin to soils/sediments and dissolved organic material will occur. Pavlou (1980) estimates that sorption of nonpolar hydrophobic pesticides is very high; therefore little environmental mobility would be expected for these compounds.

Aldrin evaporates rapidly from aquatic environments and soil. Photolysis occurs in aqueous solution or on plant surfaces, with conversion primarily to dieldrin, although a small fraction (generally less than 5 percent) is slowly converted to photodieldrin

(Rosenblatt *et al.* 1975). Hydrolysis of dieldrin is also quite slow with a half-life in excess of 4 years (U.S. EPA, 1979).

The concentrations of aldrin and dieldrin in soils decrease over time through leaching, runoff, volatilization and degradation. Aldrin is oxidized to its epoxide dieldrin. This conversion, which appears to have a half-life of about a year, may be enhanced by microbial activity (Rosenblatt *et al.*, 1975). The half-lives of aldrin and dieldrin in soils have been estimated to be 4 and 7 years, respectively (Rosenblatt *et al.* 1975). Over 90 percent of applied dieldrin was still present in the top three inches of a loam soil after a period of 17 months (Rosenblatt *et al.*, 1975).

Microbial degradation of aldrin occurs slowly, with the main products being close derivatives (i.e., hydroxydihydroaldrin (Rosenblatt *et al.*, 1975)). Several studies (Matsumura and Boush, 1967, 1968; Matsumura *et al.*, 1968; Wedemeyer, 1968; Anderson *et al.*, 1970; Matsumura, 1972; Fries, 1972) have shown that dieldrin too is degraded over time by microbial action in soil, resulting in non-toxic metabolites. The significance of environmental degradative processes is indicated by the fact that levels of these compounds in the environment and diet have been steadily decreasing since 1974, when their use was suspended for agricultural applications in the U.S. Furthermore, according to the National Human Adipose Tissue Survey database, aldrin/dieldrin levels in autopsy fat samples have shown a steady decline over the past decade. In the absence of further agricultural use of aldrin/dieldrin, the observed decline in existing soil concentrations of dieldrin can be expected to continue. Human exposure to dieldrin can therefore be expected to decline over time.

Uptake of dieldrin in plants is variable. For example, potatoes grown in dieldrin-treated soil had concentrations almost twice as high as soil levels (Jelekar *et al.* 1983), while peeled beets had levels only one third the concentration in soil (Kohli *et al.* 1973). Concentrations in pasture crops appear to be less than the concentrations of the soil in

which they were grown (Chawla *et al.* 1981). Further data are presently being evaluated.

A range of experimental and estimated bioconcentration factors (BCFs) for aldrin and dieldrin is also reported above. ASTM (1985) indicates that chemicals with bioconcentration factors less than approximately 100 have low potential for causing harm to wildlife and human health via biomagnification of residues up food chains. The magnitude of the bioconcentration factors suggest that appreciable bioconcentration and biomagnification of aldrin/dieldrin residues may occur.

METABOLISM AND TOXICOKINETICS

Summary of Metabolism Data

Extensive data have been published on the metabolism of aldrin and dieldrin. Shell has also developed its own working summary (Shell, 1984). Aldrin is rapidly oxidized to dieldrin in both plants and animals (including humans). Dieldrin is slowly metabolized to more hydrophilic compounds which are excreted via feces and urine. There is no evidence of significant qualitative differences in metabolites formed in different animal species, including humans. The major metabolite of dieldrin in most species is 9-hydroxydieldrin, with lesser amounts of 6,7-*trans*-dihydroxydihydroaldrin, its dicarboxylic acid derivative and the bridged pentachloroketone formed in species-specific ratios.

The data base is incomplete, however, as not all the metabolites which have been identified have been sought in the species which have been examined for toxicity. The major animal metabolites, 9-hydroxy dieldrin, the pentachloroketone and the 6,7-diol, have also been identified in humans. None of these metabolites have been shown to possess biological activity approaching that of dieldrin itself.

Absorption and Distribution

Aldrin and dieldrin are absorbed into the body from the alimentary tract, through the skin or by inhalation of the vapor or dust. Aldrin is rapidly converted to dieldrin in the body, and exposure to either compound results in almost immediate elevation of dieldrin levels in the blood. Dieldrin in blood is rapidly stored, predominantly in fatty tissues, from which it slowly re-enters the blood over time and is detoxified in the liver and excreted. The typical distribution ratio for (dieldrin in adipose tissue/dieldrin in blood) is 136 under equilibrium conditions of intake, storage, and elimination (Hunter and Robinson, 1967; Hunter *et al.*, 1969), indicating the large storage capacity of fat for this material. Since dieldrin is taken up very rapidly, especially in fatty tissues, and since the biological half-life of dieldrin is very long (approximately 9 months in humans) the levels in blood are quite stable and representative of total body burden. With continuous exposure to aldrin (or dieldrin), the rate of elimination gradually increases until a steady state is achieved at about 21 to 24 months.

Steady State Concentrations

When a steady state is reached between intake and excretion, the amount of dieldrin found in specific tissues reflects the total amount absorbed regardless of the route of absorption. The ratio of dieldrin intake (e.g., ppm in food) to the concentration found in various tissue has been determined for several species, including the human. It is possible, therefore, to estimate daily exposures from tissue concentrations and, conversely, the tissue concentrations in different organs at given dietary exposures. NIOSH (1978) summarized some of these data for different species.

Biological Half-Life

Since dieldrin is only slowly metabolized and excreted, it accumulates in the body. Available information leads to the conclusion that with continuous exposure, a plateau is reached for concentrations found in the various body tissues -- an approximation being that 95% of the maximum for a particular intake would be reached in a time interval of three times the excretion half-life. There are data for half-lives of dieldrin in many

species, including man. Many of these data were summarized by Moriarty (1975), and include the following:

TABLE 1.

Biological Half-Life of Dieldrin in Several Species

Species	Biological half-life (days)
Laboratory rat	5 - 15
Pigeon	47
Steers and heifers	74
Ewes	97
Beagle dogs	126 - 164
Human	266

Correlation of Dieldrin Blood Levels With Exposure and Effects

Symptoms of aldrin/dieldrin intoxication are non-specific, and thus a differential diagnostic test is required to confirm that symptoms, signs and clinical course of any particular case are the result of aldrin/dieldrin intoxication. Extensive work, including animal studies, medical surveillance of workers employed in the manufacture or formulation of aldrin/dieldrin, and human volunteer studies, has demonstrated that the adverse effects caused by aldrin/dieldrin are directly related to the concentration of dieldrin in the blood (Brown *et al.*, 1964; Hunter and Robinson, 1967; Hunter *et al.*, 1969; Jager, 1970). Thus, determination of dieldrin levels in blood provides a powerful, convenient and reliable differential diagnostic aid. Further, since data have been reported on dieldrin levels in blood as well as various tissues and organs of both animals and humans, it is possible to extrapolate from one route of exposure to any other route, and to determine rather precisely what the total exposure to aldrin/dieldrin has been. It should also be pointed out that dieldrin blood levels are more reliable, useful and definitive indicators of actual exposure than human diet estimates.

Because of the convenience and early demonstration of the value of blood monitoring, it has been possible to correlate blood levels with specific observed effects following exposure to aldrin/ dieldrin. Jager (1970) showed that no objective clinical or laboratory indications of adverse effect were seen in workers whose blood dieldrin levels were less than 200 ng/ml (0.2 ug/ml). Further discussion of blood levels with specific effects follows as appropriate in this document.

TOXIC EFFECTS OF ALDRIN/DIELDRIN

There is a considerable body of information on the toxicity of aldrin and dieldrin derived from studies of laboratory animals, domestic animals, and humans under both laboratory and practical conditions. This data base includes reports and papers published thirty to forty years ago, when dieldrin was used for public health purposes and also for the treatment of external parasites in domestic animals.

Acute Toxicity

Both aldrin and dieldrin are acutely toxic to animals and humans. The oral LD_{50}s for aldrin and dieldrin in rats are 39-60 mg/kg and 46 mg/kg, respectively (Merck, 1983). The dermal LD_{50} for both aldrin and dieldrin is approximately 100 mg/kg. No information suggests that there are any major species differences in the acute toxicity of aldrin and dieldrin.

Major Target Organs and Systems for Aldrin/Dieldrin

Available animal and human evidence points to the central nervous system (CNS) as the main target organ for acute toxic effects of aldrin/dieldrin. These effects, including hyperexcitability, tremors, convulsions and possibly death from anoxia, are thought to be due to a generalized overstimulation of synapses. Liver is also a target organ in many species, responding with hypertrophy and/or enzyme induction in a species-specific manner. Mice appear to be more susceptible than other species with respect to liver lesions. Dieldrin-induced immunosuppression has been observed in mice (e.g. Krzystyniak *et al.* 1989) and several other species (Wassermann *et al.* 1972; Kaminski

et al. 1982), but this effect has not been noted in humans. In general, liver is the most sensitive target, showing reversible changes (e.g. hepatomegaly, enzyme induction) at levels of exposure that have no detectable effect on the CNS.

Central Nervous System

Acute or long-term overexposure to aldrin and dieldrin produces effects ranging from apprehension and excitability to involuntary muscle movements and epileptiform convulsions in all mammalian species that have been studied. These effects are caused by global intensification of synaptic activity, apparently due to inhibition of GABAergic transmission (Woolley *et al.*, 1985).

Some of the studies relating to the CNS have been summarized by Taylor and Calabrese (1979). In humans, exposure to high levels of aldrin/dieldrin produces electroencephalographic (EEG) anomalies (Spiotta, 1951; Hoogendam *et al.*, 1962, 1965; Kazantzis *et al.*, 1964; Jager, 1970; Gupta, 1975). Jager (1970) described the EEG changes as consisting of bilateral peak and dome complexes which did not occur when dieldrin blood levels were below 0.2 ug/ml. The EEG anomalies he described had disappeared within a few weeks or months after exposures were discontinued.

Garrettson and Curley (1969) reported a parallelism between the rate of disappearance of EEG changes and the rate of decrease in dieldrin blood levels in the case of an accidentally poisoned child. Now, blood analysis has supplanted EEG examination as the method of choice for monitoring exposed persons. Based on studies with exposed workers, Brown *et al.* (1964) concluded that a blood dieldrin concentration of 150-200 ug/l is the threshold for CNS effects. This level is supported by other human data reported by Avar and Czegledi-Janko (1970) and Kazantzis *et al.* (1964).

Those who survive recover completely after a short period of residual symptoms and signs (Hoogendam *et al.*, 1962; Jager, 1970; Avar and Czegledi-Janko, 1970). Rare

cases have been reported in which some unusual sequelae were alleged to be due to aldrin/dieldrin poisoning, but in each of these cases, the connection to aldrin/dieldrin was circumstantial, the exposure had not been high, no analyses of dieldrin concentrations in blood or fat were reported and the symptoms reported were different from and not typical of results from animal experiments. Importantly, in humans, even at exposures which caused clinical signs of CNS effect, there were no observed effects on any other organ system.

Liver

There are distinct species differences in liver responses to aldrin/dieldrin, including increased liver-to-body weight ratios, induction of hepatic drug metabolizing enzymes and neoplasia (Wright *et al.* 1972, 1977, 1978).

Enzyme Induction

Animal Studies

The earliest, most sensitive response to aldrin/dieldrin exposure in many species is the proliferation of hepatic smooth endoplasmic reticulum and the induction of several drug metabolizing enzymes, including the microsomal cytochrome P-450-dependent monooxygenases. These inductions may serve to increase or decrease the toxicity of a given xenobiotic, since specific enzymatic activities can either detoxify or bioactivate not only the inducing compound but others which may also be present.

In addition to enzyme induction, mouse liver tissue responds with organ weight and structural changes that are visible under light or electron microscopy. In the Wright *et al.* studies cited above, primates did not show increased liver weights following dieldrin, whereas mice did. Other primate studies (Adamson and Sieber, 1983) further highlighted the differences between rodents and primates with regard to hepatic responses to organochlorines.

Human Studies

Most significantly, a number of human studies have shown no evidence of alterations in liver structure or function, including enzyme induction, in exposed manufacturing and agricultural workers and volunteers who were examined specifically for this endpoint. Many reports (Hunter *et al.*, 1969; Jager, 1970; Warnick and Carter, 1972; Morgan and Roan, 1974; Ottevanger and van Sittert, 1979; Sandifer *et al.*, 1981; van Sittert and de Jong, 1987) have shown that no liver enzyme induction occurs in humans with blood dieldrin levels at or below 105 ng/ml (0.1 ug/ml). Using a 10-fold safety factor to extrapolate to the general population, a safe blood dieldrin level of 10 ng/ml (0.01 ug/ml) has been used. It should also be noted that a no observed adverse effect (NOAEL) blood dieldrin level of 20 ng/ml (0.02 ug/ml) has been determined for humans.

Neoplasia

On the basis of the criteria proposed by the Carcinogen Assessment Group (CAG) of the U.S. EPA for evaluating the overall weight of evidence for carcinogenicity to humans, both aldrin and dieldrin are classified as Group B2 carcinogens (probable human carcinogens) (U.S. EPA, 1989) due to their hepatocarcinogenicity in mice.

Mice

Aldrin/dieldrin have been tested extensively for carcinogenic potential in mice (Davis and Fitzhugh, 1962; Walker *et al.*, 1972; Hunt *et al.*, 1975; Thorpe and Walker, 1973; Epstein, 1975; National Cancer Institute (NCI), 1978; Dix, 1981; Meierhenry *et al.*, 1981; Tennekes *et al.*, 1982). The results of several of these studies are summarized below; the consensus from these data is that aldrin/ dieldrin cause tumors in mouse liver, but no other tissue.

The early studies of aldrin and dieldrin by Davis and Fitzhugh (1962) used only one dose level, 10 ppm, and were not conducted according to current standards, but showed that aldrin and dieldrin caused tumors in mouse livers. The Walker *et al.* studies (1972) were

well designed and conducted. CF1 mice were treated at multiple dose levels (0.1, 1 and 10 ppm) over their lifetimes, and a dose-response relationship for liver tumors established. A smaller number of mice were exposed to dieldrin levels of 1.25, 2.5, 5, 10 and 20 ppm to further define the dose-response relationship. Tennekes *et al.* (1982) examined the results of the Walker *et al.* studies and concluded that the dose-response for dieldrin supported the concept that it acted as a promoter rather than an initiator of liver tumors in mice. A reversibility study done by Walker *et al.* (1972) showed a regression of non-tumorigenic effects (hepatomegaly and cytoplasmic changes) and a reduced incidence of type B tumors after cessation of exposure, although once liver tumors appeared they did not regress. This observation is also consistent with a promotional mechanism of carcinogenesis.

NCI (1978) conducted a bioassay in B6C3F1 mice at 2.5 and 5 ppm dieldrin in the diet for 80 weeks, with an additional observation period of 13 weeks. This study was also well designed and conducted, and confirmed a dose-related increase in hepatocellular carcinomas in males, but not in females.

Other studies on various strains of mice (C3HeB/Fe, C3H, CF1, B6C3F1, and C57BL/6J) confirm that dieldrin causes liver tumors in mice (Thorpe and Walker, 1973; Hunt *et al.*, 1975; Epstein, 1975; Dix, 1981; Meierhenry *et al.*, 1981; Tennekes *et al.*, 1982).

Rats

A number of rat studies involving both aldrin (Borgmann *et al.*, 1952; Treon and Cleveland, 1955; Deichmann *et al.*, 1967, 1970, 1979; NCI, 1978a) and dieldrin (Treon and Cleveland, 1955; Fitzhugh *et al.*, 1964; Deichmann *et al.*, 1970, 1979; NCI, 1977, 1978a, 1978b; Walker *et al.*, 1969) have been done. In general, liver changes typical of chlorinated hydrocarbon insecticide rodent liver (CHIRL) were seen, including enlarged centrilobular hepatocytes with somewhat increased cytoplasmic oxyphilia and

peripheral migration of the basophilic granules. However, no increase in liver tumors was observed in any of the studies.

The NCI studies were considered to be the best designed and conducted; others suffered from excessive dosing, high mortality, short duration and inadequate pathologic evaluations. The histopathology for three of the rat studies was reevaluated by Reuber- (cited in Epstein, 1975) and Stevenson *et al.* (1976. Reevaluation of the Fitzhugh *et al.* (1964) data showed an inverse dose-response relationship, with 5/18 rats (4/7 females and 1/11 males) fed 100 ppm dieldrin having hepatocellular carcinomas, but only 3/11 rats at 150 ppm (Epstein, 1975). The 100 ppm response was significant at $P < 0.03$ for combined males and females, but 150 ppm was not. None of the other studies substantiated this finding, and it is considered to be highly questionable.

Hamsters

In a hamster study, Cabral *et al.* (1979) reported that Syrian hamsters could tolerate dietary exposures of dieldrin up to 180 ppm with no evidence of increased incidence of liver tumors.

Dogs

Hypertrophy of individual liver cells caused liver enlargement in dieldrin-treated dogs, with some evidence of organelle changes similar to those found in the rat (Wright *et al.* 1972, 1977, 1978). Regression of the liver effects following cessation of exposure occurred more slowly than in the rat, possibly due to the longer half-life of dieldrin in the dog. No liver tumors were observed.

Monkeys

There was little detectable increase in liver weight or evidence of hypertrophy in the monkey, although the dieldrin tissue concentrations were above those associated with a response in other species (Wright *et al.* 1972, 1977, 1978). The effects of feeding diets containing 0, 0.01, 0.1, 0.5, 1.0, 1.76 or 5 ppm dieldrin (0.0002 - 0.07 mg/kg/day) to

male rhesus monkeys for approximately six years was studied. As two monkeys at the highest dose level died, this level was reduced.

Although the livers of test monkeys contained higher levels of dieldrin than did those of rodents receiving similar concentrations in the diet, monkey liver response was less marked. There was no evidence of liver enlargement or histological changes, including neoplastic or preneoplastic changes, associated with dieldrin exposure. The liver microsomal monooxygenase system was induced in Rhesus monkeys fed dieldrin at dietary levels of 1.0 ppm and above for 6 years. However, the toxicological significance of this induction is unclear.

Genotoxicity

Aldrin and, to a greater extent, dieldrin have been the subjects of many genotoxicity studies, including investigations of gene mutation, chromosome aberrations, and epigenetic mechanisms of carcinogenesis. As a result of these studies, both pesticides are considered to be non-genotoxic. Much of the data has been reviewed by Ashwood-Smith (1981). The validity of each study which reported an adverse effect of aldrin/dieldrin has been questioned on grounds of inadequate experimental design, technical problems or use of inappropriately high (cytotoxic) doses. All *in vivo* studies have been negative.

Dieldrin was negative in a mouse dominant lethal assay (Epstein *et al.*, 1972) and a mitotic gene conversion assay (Dean *et al.*, 1975). Haworth *et al.* (1983), Glatt *et al.* (1983), Marshall *et al.* (1976) and DeFlora *et al.* (1984) all reported negative results in mutagenicity studies. Majumdar *et al.* (1977) reported positive results, but this study is flawed by their failure to include positive controls and inconsistent results in the solvent controls. Ahmed *et al.* (1977a) also reported positive results, but these workers failed to use S9 fraction and encountered cytotoxicity at the higher doses.

Majumdar *et al.* (1976) conducted an *in vitro* chromosomal aberration study with human lung cells and found dose-dependent increases in aberrations. However, dose-related cytotoxicity was also observed, making the study results inconclusive.

Probst *et al.* (1981) and Klaunig *et al.* (1984) reported negative results in unscheduled DNA synthesis studies. Ahmed *et al.* (1977b) observed unscheduled DNA synthesis, but their data were qualitative only, and there were critical technical flaws in both study design and performance.

Dieldrin caused inhibition of gap junction intercellular communication in Chinese hamster cells, an effect typical of many tumor promoters (Kurata *et al.*, 1982; Trosko *et al.*, 1987). Wade *et al.* (1986) used a different technique and different mammalian cell line to investigate the same phenomenon.

Mechanism of Aldrin/Dieldrin Carcinogenicity

Stevenson and Walker (1969) suggested that there might be a relationship between hepatic enzyme induction and liver tumors, a view still regarded as plausible (Newberne, 1986; Diwan, 1986). However, this connection cannot be made indiscriminately, as there are also many enzyme-inducing compounds, including human drugs such as the diazepams, which cause tumors in mice but not in humans. Ramel *et al.* (1986) speculated that free radical formation might be involved in the development of murine liver tumors caused by dieldrin and other non-genotoxic inducers of mouse liver hyperplasia. There is an increasing body of experimental information which supports this view, although the mechanism has not yet been elucidated (Ruch and Klaunig, 1986).

The significance of liver tumors in mice is a highly controversial matter and there is much debate on this point, particularly where there is no other tumor response and where no genotoxicity can be demonstrated. For reasons discussed in greater detail below, use

of the mouse liver tumor response as a basis for quantitative risk assessment for aldrin/dieldrin in the human may not be appropriate.

Teratology/Developmental Toxicity

Studies in several species have indicated that aldrin/dieldrin are not teratogenic at doses that do not cause overt maternal toxicity (mice: Ottolenghi *et al.*, 1974, Chernoff *et al.*, 1975, Dix *et al.*, 1978, Costella and Virgo, 1980; rabbits: Dix and Wilson, 1971; rats: Chernoff *et al.*, 1975, Coulston *et al.*, 1980; hamsters: Ottolenghi *et al.*, 1974).

Costella and Virgo (1980) showed that both aldrin and dieldrin were fetotoxic at doses which were also maternally toxic. Ottolenghi *et al.* (1974) exposed pregnant Syrian golden hamsters and CD1 mice to a dose of half the LD_{50} on day 7, 8 or 9 of gestation, and observed reduced fetal weight, increased fetal mortality and increased abnormalities (cleft palate, open eye, webbed feet) in hamsters, and abnormalities in mice. However, the significance of these results is questionable, as the study design does not conform to current U.S. EPA and Organization for Economic Cooperation and Development (OECD) guidelines or standard practice.

Reproductive Toxicity

Animal Studies

Adverse reproductive effects associated with aldrin and dieldrin in animals, primarily decreased litter size and increased postnatal mortality, have only been reported at doses which also produce maternal toxicity.

Mice

Virgo and Bellward (1975, 1977) conducted two studies with Swiss-Vancouver mice. Doses of 2.5, 5, 10, 15, 20 or 25 ppm in the diet were administered in the first study, and 5, 10 and 15 ppm in the second, starting 4 weeks prior to the second mating and continuing until day 28 post partum. In the first study, pre-weaning pup mortality was increased at all dose levels. No gross abnormalities were seen in any pups, and no pups

had tremors or convulsions. Significant maternal mortality was seen at 20 and 25 ppm. No major behavioral changes were seen in dams fed 5 or 10 ppm dieldrin other than a delayed time to start nursing, but dams showed hyperactivity at 10 ppm and above. This hyperactivity apparently contributed to the high pup mortality. Decreased fertility was seen at 10 and 15 ppm (but not at higher doses), and decreased litter size at 25 ppm. In the second study, there was a dose-related decrease in pup viability at 48 hours. Litter loss was found to correlate with aldrin/dieldrin-induced maternal hepatomegaly.

No effects were seen on fecundity, gestation period or litter size of Swiss mice fed dieldrin at 5 mg/kg for 20 days prior to mating (Good and Ware, 1969) or at 3 ppm in the diet for 6 generations (Keplinger *et al.*, 1968).

Rats

Treon and Cleveland (1955) fed groups of rats aldrin or dieldrin at levels of 2.5, 12.5 and 25 ppm for three generations. A reduced number of pregnancies at the first mating (but not in subsequent generations) was reported at 12.5 and 25 ppm aldrin and at all three doses of dieldrin. A marked increase in pre-weaning pup mortality was seen at 12.5 and 25 ppm for both compounds. Neither material had any adverse effect on reproductive capacity. The LOAEL was 2.5 ppm; a NOAEL was not established.

Eisenlord (1967) observed no adverse effects in a three-generation study of rats fed doses of 0.01, 1 and 2 ppm dieldrin in the diet. Harr (1970) conducted a two-generation study in Wistar rats, with doses ranging from 0.08 ppm to 40 ppm in the diet; 10 per group were mated at 146 days. There were maternal deaths at 20 and 40 ppm, and no dose-response for fertility or litter size. Preweaning deaths from convulsions or starvation were seen in pups from mothers fed 2.5 ppm or higher, but not from those fed 1.25 ppm or lower. The no-effect level was 1.25 ppm. This study had major design and conduct deficiencies and is considered of questionable value.

Coulston (1980) conducted a single generation study in rats administered 4 mg/kg from day 15 of gestation through 20 days post partum. No adverse effects and no malformations were seen.

Dogs

Kitselman (1953) studied dogs fed 0.2, 0.6 and 2.0 mg/kg aldrin or dieldrin for one-year. Survival of pups was decreased and histologic examination of the pups revealed hepatic and renal degenerative changes; liver changes were also seen in the mothers. The size of the study was too limited to delineate dose-response relationships, but 0.2 mg/kg was a no-effect level.

Deichmann (1971) dosed beagle dogs with 0.15 or 0.3 mg/kg/day aldrin for 14 months and observed subnormal reproductive performance up to 16 months after dosing was stopped.

Humans

Transplacental transfer of dieldrin from mother to the fetus is known to occur (O'Leary *et al.*, 1970; D'Ercole *et al.*, 1976; Polishuk *et al.*, 1977; Saxena *et al.*, 1980), but no adverse fetal effects have been correlated with its presence. Curley *et al.* (1969) measured the concentration of dieldrin in various tissues of stillborn infants and in the cord blood of normal-term infants. Levels in adipose and major organ tissues of stillborns were in the same range as that reported for the general adult population of the U.S.; dieldrin levels did not correlate with either known or unknown cause of death. Levels in the cord blood of normal-term infants were within the range previously reported for human blood (Dale *et al.*, 1966).

A study carried out in India by Saxena *et al.* (1983) is the only human study suggesting potential reproductive effects of aldrin/dieldrin. However, this study has major analytical, statistical and procedural deficiencies which render the results uninterpretable.

Inhalation Toxicity

Inhalation is a much less important route of exposure for aldrin/dieldrin than ingestion. As is true for other exposure routes, inhaled aldrin is rapidly converted to dieldrin, which is rapidly distributed throughout the body via the blood. Dieldrin has very low volatility, with a vapor pressure of 3.1×10^{-6} mm Hg at 20 degrees C, and a saturated vapor concentration of 0.004 ppm (63 ug/m^3). Aldrin is slightly more volatile, with a vapor pressure of 7.5×10^{-5} mm Hg at 20 degrees C, and a saturated vapor concentration of 0.099 ppm (1.47 mg/m^3). Based on these concentrations, and the known acute toxicity, it is unlikely that a toxic concentration by inhalation alone could be attained for either compound.

Animal Inhalation Studies

Rats were exposed to air containing 2-3 mg/l dust of technical aldrin or dieldrin for 1 hour and observed for 48 hours to determine Class B Poison Labelling and Packaging requirements of the Bureau of Explosives (Anderson, 1951-1954). Less than 10% mortality occurred with each material.

A study of rats exposed to air containing 1-2 mg/l of formulated products and observed for 48 hours (Anderson, 1951-1954) gave the results shown in Table 2.

TABLE 2.

Rat Mortality Following Inhalation of Aldrin or Dieldrin

Formulation	% Mortality
85% dieldrin wettable powder	10
65% aldrin wettable powder	<50
60% aldrin emulsifiable concentrate	<50

The acute 4-hour LC_{50} for rats exposed to aqueous dilutions of a 48% (w/v) emulsifiable concentrate of aldrin as an aerosol was estimated to be equivalent to 3% (w/v) aldrin aerosol (Macdonald, 1982). Median droplet size was 52 micrometers, and although the rats were exposed "nose only," observed

grooming of the face after exposure and the large droplet size suggest that ingestion was a significant contributory factor.

Mice, hamsters and guinea pigs exposed to vaporized aldrin at 0.5 g/1000 cubic feet of air (18 mg/m^3) for 178 days showed no adverse effects (Baker *et al.*, 1959).

Human Inhalation Studies

Human volunteers were exposed to levels of 1.31 and 15.5 ug/m^3 aldrin vapor in air for 60 minutes (Bragt *et al.*, 1984). Medical follow-up showed no adverse effects in any subjects. It was determined that approximately 50% of the inhaled aldrin vapor was absorbed and retained. It has been determined that a concentration of 6-10 ug/m^3 aldrin is a no-observed-effect level of exposure, with resulting dieldrin blood levels still being at or below a no-observed-effect level for the general population. Based on the demonstrated human no-observed-effect blood level of 0.01 ug/ml, assuming 12 cubic meters of air are inhaled per day with 100% retention (very conservative; actual data have shown approximately 50% retention is more realistic (Beyermann and Eckrich, 1973)), exposure to 10 ug/m^3 continuously for 21 to 24 months would be required to attain the blood level of 0.01 ug/ml. This means the daily intake would be 12 m^3 x 10 ug/m^3 = 120 ug, the human no-effect level derived from the volunteer and worker studies, using a safety factor of 10.

Toxicity to Wildlife and Domestic Animals

Aquatic Organisms

Aldrin and dieldrin are both acutely toxic to freshwater species at low concentrations. Tests in fish showed that the two chemicals had similar toxicities, with LC_{50} values ranging from 1 to 46 ug/liter for different species. Final acute values (i.e., the concentrations of material protecting 95 percent of the organisms (U.S. EPA, 1980)) for freshwater species were determined to be 2.5 ug/liter for

dieldrin and 3.0 ug/liter for aldrin. Saltwater species were also quite sensitive to aldrin and dieldrin. The range of LC_{50} values was similar to that for freshwater species: 2 to 100 ug/liter for aldrin and 1 to 34 ug/liter for dieldrin. The saltwater Final Acute Values were 1.3 ug/liter for aldrin and 0.71 ug/liter for dieldrin.

Chronic studies of the effects of dieldrin on freshwater and saltwater species have also been conducted. For freshwater organisms, chronic values as low as 0.2 ug/liter were obtained. The Final Acute-Chronic Ratio was determined to be 8.5, and the calculated Freshwater Final Chronic Value is 0.29 ug/liter. Only one chronic study was done on saltwater species. Therefore, the saltwater Final Chronic Value of 0.084 mg/liter was determined by dividing the Final Acute Value by the Acute-Chronic ratio.

No chronic studies were identified for aldrin, but because its acute toxicity is comparable to that of dieldrin and because it is rapidly converted to dieldrin in animals and in the environment, it likely exhibits chronic toxicity as well.

Wild and Domestic Birds and Mammals

Both compounds, but especially dieldrin, have been associated with large-scale bird and animal kills in treated areas. The LD_{50}s of aldrin and dieldrin in several species are listed in Table 3.

TABLE 3.

Orals LD_{50}s of Aldrin and Dieldrin in Wild and Domestic Birds and Mammals*

Species	Oral LD_{50} (mg/kg)	
	Aldrin	Dieldrin
Avian		
Mallard duck	520	381
Pheasant	16.8	79
Bobwhite quail	6.59	–
California quail	–	<9.0
Mammalian		
Mule deer	18.8-37.5	75-150
Goat	–	100-200

*Data from Hudson *et al.* (1984)

Epidemiology Data

As discussed previously, while the earliest and most sensitive effect of aldrin/dieldrin in many animal species is induction of liver microsomal mixed function oxygenase enzymes (Wright *et al.*, 1972), it has been well documented in studies with long-term exposed humans (volunteers, manufacturing and formulation workers and agricultural workers) that these changes do not occur in humans (Hunter *et al.*, 1969; Jager, 1970; Warnick and Carter, 1972; Morgan and Roan, 1974; Ottevanger and van Sittert, 1979; Sandifer *et al.*, 1981).

In a recent study of occupationally exposed humans, liver function of aldrin/dieldrin workers showed no changes associated with exposure to these materials, even in those workers with the most extensive exposure (van Sittert and de Jong, 1987). There were 100 exposed workers in the study, with 29 in the group with the highest exposures and 808 non-exposed office workers in the

control group. In the group of aldrin/dieldrin workers with longest duration of employment (median: 21.6 yrs; range: 7.1 to 26.6 yrs), the highest personal total aldrin + dieldrin intake (median: 1260 mg; range: 777 to 5758 mg), and the highest personal daily intake (median: 209 ug/person/day; range: 103 to 941 ug/person/day), there were no statistically significant differences in serum levels of alkaline phosphatase, alanine aminotransferase, lactate dehydrogenase, and gamma glutamyl transferase or in urinary levels of glucaric acid compared to the large control group. Serum gamma glutamyl transferase was slightly increased compared to controls, but all results outside the upper reference limit could be explained by the individuals' medical histories. In addition, the four workers with the highest average personal daily intake over their total exposure period (range: 464-941 ug/person/day), with a total absorbed dose of aldrin + dieldrin ranging from 2219 to 5758 mg, showed no abnormalities in any liver function parameter. The authors concluded that "long-term occupational exposures to aldrin and dieldrin, up to 941 ug/person/day and up to a personal total intake of 5758 mg, did not produce detectable liver damage or hepatic enzyme induction."

The workers in the above-described study are also included in an ongoing study of more than 1000 workers exposed to aldrin and/or dieldrin (Jager, 1970; Versteeg and Jager, 1973; van Raalte, 1977; and most recently Ribbens, 1985). Although many of these individuals had high exposure and have been observed for more than 25 years, no increase in the incidence of liver cancer among them has been observed. In the most recently published update on mortality from this group of workers (Ribbens, 1985), the observed total mortality of a sub-group of 232 men with long-term exposure (mean = 11 years; range 4-27 years) to high concentrations and with long observation times (mean = 24 years; range 4-29 years) was 25, "significantly lower than the expected number of 38" for the study group.

This study is now being updated again (de Jong (1990) presented to the U.S. EPA on April 10, 1990). The mortality and exposure components of this most recent follow-up were reviewed by a panel at Georgetown University in October, 1989, which concluded that the study had been carried out according to accepted procedures and hence could provide a basis for comparison of the carcinogenic and toxic effects of aldrin/dieldrin exposure on mice versus humans. A draft of this section (Chapter 5 in de Jong, 1990) reflects certain comments made by the Georgetown peer review panel. It is important to note that the de Jong study (1990) is superior to its predecessors in two significant respects:
(1) the follow-up interval following cessation of exposure is longer; and (2) it incorporates a biological monitoring study which permits estimation of personal exposures during the period of exposure, and hence delineation of dose-response relationships. Notably, with the observation period extended up to 1987 (35 years), no statistically significant increased risk was found for any of the site-specific cancers examined in the exposed groups. A preliminary statistical analysis of these data (Sielken (1990) also presented to EPA on April 10, 1990) indicated an apparent dose-related decrease in cancer incidence. The significance of the observed decrease is currently under study. Sielken also compared the mouse and human data and concluded that the available evidence suggests that they are not compatible.

A similar study done on workers from four pesticide plants in the United States (Ditraglia *et al.*, 1981) also found deaths to be fewer than the expected number from all causes. Another report (Hayes and Curley, 1968) presented a correlation of exposures and dieldrin levels in plasma, fat and urine from workers at one of these plants (the Rocky Mountain Arsenal). This report concluded that dieldrin levels were more related to total exposure than to either high or low recent exposures, and that there was no relationship between dieldrin levels found and the use of sick leave for the workers.

Discussion of Epidemiological Data

The importance of regular updating for relevant epidemiology studies becomes evident as each additional few years of observation provide increasingly valuable information. For instance, at the time of the U.S. EPA Hearings on dieldrin in 1974, the Shell experience at Pernis was based on an exposure period of about 20 years. Now that experience covers a period of 35 years and is continuing. As mentioned above, a major update of the data for these subjects is presently in progress (De Jong, 1990), and the results were subjected to peer review prior to publication. Since this population had a high initial exposure, it seems reasonable to assume that the continuing study of this population would detect any untoward effect in humans should it occur. The same comment also applies to the Ditraglia (1981) cohort (which includes the Rocky Mountain Arsenal workers), which was updated by NIOSH through 1982. Apparently, the additional six years of follow-up did not reveal any statistically significant excess in cancer deaths. It is our understanding that NIOSH plans to update these additional observations, but has not yet completed the analysis.

Although the U.S. EPA previously considered "...that there is no evidence presently available to indicate that any of the termiticides, including aldrin/dieldrin, are carcinogenic in humans" (July 19, 1983, letter from Edwin Johnson, former Director of U.S. EPA Office of Pesticide Programs, to Roger Strelow, who had written to Johnson as counsel for Shell International Chemical Company), its Cancer Assessment Group (CAG) has reclassified aldrin/dieldrin as B2, a probable human carcinogen (sufficient evidence of carcinogenicity in animals, inadequate evidence of carcinogenicity in humans) on the basis of the mouse tumor response (U.S. EPA, 1989 (IRIS)). In this estimation of the human risk of these compounds it differs with the World Health Organization (WHO), the national Toxicology Program (NTP) of the U.S. Department of Health and Human Services, and the International Agency for Research on Cancer (IARC).

IARC classified aldrin/dieldrin in Group 3, "the agent is not classifiable as to its carcinogenicity in humans; agents are placed in this category when they do not fall into any other group," in 1982 and again in 1987 (IARC, 1982, 1987). The IARC Group 3 classification corresponds to an U.S. EPA ranking of Group C ("possible human carcinogen" -- limited evidence in animals and absence of human data) or Group D ("not classified" -- inadequate animal data).

On the basis of the available animal and human data, neither aldrin nor dieldrin are classified as "known" or "reasonably anticipated to be" carcinogens by the NTP (1989).

The WHO Expert Committee on Pesticide Residues (Food and Agricultural Organization [FAO]/WHO, 1978) agreed that aldrin and dieldrin did not present carcinogenic hazard to humans, stating: "These new findings again support the view that dieldrin and aldrin are not carcinogens on the basis of the knowledge available to the meeting." This position was recently reaffirmed in the report of a task group on aldrin/dieldrin by the International Programme on Chemical Safety, which concluded that "all the available information on aldrin and dieldrin taken together, including studies on human beings, supports the view that for practical purposes, these chemicals make very little contribution, if any, to the incidence of cancer in man" (WHO, 1989).

REGULATIONS AND STANDARDS

Ambient Water Quality Criteria (U.S. EPA, 1986)

Aquatic Life (Freshwater)

Acute Toxicity:	**Aldrin:**	3.0 ug/liter
	Dieldrin:	2.5 pg/liter
Chronic toxicity:	**Aldrin:**	No available data
	Dieldrin:	0.0019 ug/liter

Aquatic Life (Saltwater)

Acute Toxicity: Aldrin: 1.3 pg/liter
Dieldrin: 0.71 pg/liter

Chronic toxicity: Aldrin: No available data
Dieldrin: 0.0019 ug/liter

Due to the presumed carcinogenicity of both aldrin and dieldrin, the ambient water criterion for both compounds is zero. Estimates of the carcinogenicity risks due to ingestion of contaminated water and contaminated organisms are listed in Table 4.

TABLE 4.

Estimated Risks of Carcinogenicity due to Contamination of Water with Aldrin/Dieldrin

Risk	Concentration (ng/liter) Aldrin	Dieldrin
10^{-4}	7.4	7.1
10^{-5}	0.74	0.71
10^{-6}	0.074	0.074

CAG Potency Slope for oral exposure (U.S. EPA, 1989):

Aldrin: 17 $(mg/kg/day)^{-1}$
Dieldrin: 16 $(mg/kg/day)^{-1}$

ACGIH Threshold Limit Value: $TWA^{1*} = 0.25\ mg/m^3$
$STEL^{**} = 0.74\ mg/m^3$

OSHA standard (air): $TWA^{*} = 250\ pg/m^3$

[1] Applies to both aldrin and dieldrin
* Time Weighted Average
** Short Term Exposure Level

RANGE OF D_T VALUES

CAG-Based D_T VALUES

The D_T value is defined as that contaminant intake rate (mg/kg/day) that should not induce any adverse effect on human health or pose a risk of cancer occurrence greater than a predetermined risk level.

The U.S. EPA CAG's cancer potency slope derived using the linearized multistage model on mouse liver tumor data was used to determine the D_T values for aldrin/dieldrin used in the Human Health Exposure Assessment for RMA. The slopes are intended to provide a plausible upper bound of the propensity of a carcinogen to produce cancer at low doses. Calculation of a D_T using a cancer potency slope requires selection of an acceptable cancer risk level. A range of risk levels from 10^{-4} to 10^{-6} was considered for all carcinogens; therefore, ranges of D_T values are presented. Derivation of the CAG D_T values for aldrin/dieldrin are as follows:

$$D_T = \text{Risk Level/Potency Slope (mg/kg/day)}^{-1}$$

For example, in the case of aldrin,

$$D_T = 1 \times 10^{-4}/17$$
$$= 5.9 \times 10^{-6} \text{ mg/kg/day}$$

The range of CAG D_T values for aldrin/dieldrin is presented in Table 5.

TABLE 5.

U.S. EPA CAG D_T Values for Aldrin/Dieldrin at Various Risk Levels
D_Ts (mg/kg/day)

Risk	Aldrin	Dieldrin
10^{-4}	5.9×10^{-6}	6.2×10^{-6}
10^{-5}	5.9×10^{-7}	6.2×10^{-7}
10^{-6}	5.9×10^{-8}	6.2×10^{-8}

Human Data-Based D_T Value

Since the mouse liver tumor response to aldrin/dieldrin is species-specific, probably represents a non-genotoxic promotional response, is considered by many to be non-predictive of the human response, and since considerable data regarding the toxicity of aldrin/dieldrin in humans are extant, an approach for determination of a D_T for aldrin/dieldrin is to base it on the available human data. A reference dose based on human data would appear to be more relevant in determining potential human risk than one based on mouse data.

Species Comparisons

The human data available from detailed observations on aldrin/dieldrin manufacturing plant workers indicates that humans are no more (and probably less) sensitive than animals with respect to the effects studied. No evidence of either enzyme induction or CNS effects has been seen in humans at intakes (on a per kg basis) even higher than those which would have produced slight but discernible effects in animals. From the data summarized above, it is possible to estimate the intakes which may be regarded as having no effect on either the CNS or the liver. Other non-cancer effects may be seen; there is no evidence, however, that other effects occur at lower intakes than those which affect the liver or CNS. The intakes which were considered to have no effect in animals are:

TABLE 6.

Dietary No-Effect Levels in Several Animal Species

Species	Dose Level (ppm)	Daily Intake (ug/kg/day)
Rat	0.10	(5)
Dog	(0.15)	5
Monkey	0.1	(5)

(data in brackets are calculated values)

Based on the two-year human volunteer studies and the ongoing monitoring program of Pernis workers cited above, the no-effect blood concentration level for humans was estimated to be 0.1 ug/ml. Liver function tests, including tests for enzyme induction, were carried out on the Pernis plant population at a time when the blood concentrations of dieldrin had fallen and no effects were seen at or below 0.105 ug/ml. Based on Hunter and colleagues' studies (Hunter and Robinson, 1967; Hunter *et al.*, 1969) relating tissue concentrations to dietary intake in a steady state condition, the blood level of 0.105 ug/ml was estimated to be equivalent to an intake of 1.22 mg/person/day for a 70-kg individual (17.4 ug/kg/day). As this intake is over 3 times higher than the no-effect intakes listed above for the rat, dog and monkey, these results suggest that humans are no more, and possibly less, sensitive to the chronic, non-carcinogenic effects of dieldrin.

Protective Daily Intake Level

The average total daily dieldrin intake (17.4 ug/kg/day) with which this blood level corresponds can therefore be regarded as an approximate no-effect intake level for the human. The 0.1 ug/ml blood level corresponds to a total daily intake of 1.221 mg/person/day (17.4 ug x 70 kg) as calculated from the mathematical relationship derived from the human volunteer study cited above. Applying a safety factor of 10 to allow for individual variation and susceptibility

results in a blood level of 0.01 ug/ml, and a corresponding daily intake of 0.12 mg/person/day for a no-effect level.

Human D_T Based on the WHO Acceptable Daily Intake (ADI)

A D_T based on the WHO ADI is 0.0001 mg/kg/day; for a 70-kg person, this corresponds to a daily intake of 0.0007 mg/person/day. This intake level is even more conservative than the human data-based number of 0.12 mg/person/day derived above.

Potential Risk Based on WHO ADI

To examine the consequences of exposure of mice to a dietary level of aldrin/dieldrin equivalent to the WHO ADI of 0.0001 mg/kg/day, estimates of tumor incidence at that dose (approximately equivalent to 0.001 ppm in feed; see NIOSH data) were extrapolated from data reported in four studies in which more than one dose of dieldrin (Walker, 1972; Hunt, 1975; NCI, 1978a) or aldrin (NCI, 1978a) was administered to mice. The Hunt et al. (1975) and Walker et al. (1972) experiments were conducted under the same conditions of housing, diet, etc. and with the same strain (CF1) and source of mouse. The main difference was the time when the study was carried out and the dose rates chosen. Table 7 summarizes the risk estimates calculated for the WHO ADI intake level using various models.

TABLE 7.

Tumorigenic Risk Level to Mice Ingesting 0.0001 mg/kg/day Aldrin or Dieldrin (0.001 ppm in the diet)

Strain/ Sex	Logit	Weibull	Multi-hit	Multi-stage	Geometric Mean	Ref.
Dieldrin						
CF1 M	1.7E-7	2.6E-5	1.5E-3	1.6E-4	3.21E-5	1
F	(1.6E-7)	(5.2E-5)	(6.6E-4)	(2.0E-4)	3.21E-5	
CF1 M	1.6E-11	2.9E-8	1.7E-12	6.5E-8	4.76E-10	2
F	6.8E-7	8.9E-6	5.7E-7	9.8E-5	4.29E-6	
B6C3F1 (M only)						
Pooled	6.2E-8	1.5E-7	5.4E-8	1.4E-5	2.9E-7	3
Matched	5.9E-7	1.4E-6	2.1E-6	3.5E-5	2.79E-6	
Aldrin						
B6C3F1 (M only)						
Pooled	1.1E-8	1.3E-7	5.9E-8	2.0E-5	2.03E-7	3
Matched	7.8E-8	8.4E-7	3.4E-8	4.3E-5	5.56E-7	

1: Hunt *et al.* (1975)
2: Walker *et al.* (1972)
3: NCI (1978a)

Also notable is the fact that in the NCI-sponsored study (NCI, 1978a) using B6C3F1 mice, the incidence of hepatocellular carcinomas (and all other tumors) in the females was not statistically significantly different in any exposed group compared to controls. Curiously, the total tumor incidence in the females at the high dose was much lower than at the low dose.

The highest estimated risk was obtained applying the the multihit model to the Hunt *et al.* (1975) data on male animals. The risk estimate derived from the

corresponding Walker *et al.* (1972) data was nine orders of magnitude less -- an indication that assessing risk on the basis of empirical models is not yet an exact science.

The NCI male mouse data (1978a), which have been used for many other risk assessments by U.S. EPA, predicts a risk which ranges from 4.3×10^{-5} to 7.8×10^{-6}, depending on the model used. From these extrapolated risk estimates, it appears that even the mouse -- the only species demonstrated to be susceptible to aldrin/dieldrin-induced carcinogenesis -- would be at very low risk for tumorigenesis at the WHO ADI.

CERTAINTY AND UNCERTAINTY IN THE ALDRIN/DIELDRIN TOXICITY AND CARCINOGENICITY DATA

The data base for aldrin/dieldrin toxicity is extensive and varied. However, when considering the risk potential associated with these chemicals, it is important to take into account the strengths and weaknesses of the information used to derive the risk estimates, and the impact these have on the degrees of certainty and/or uncertainty associated with the estimates. Some of these factors are highlighted in the following discussion.

Although animal toxicity data are very important and can be used to elucidate mechanisms of action and indicate areas of concern for human health, they cannot substitute for or supercede actual human data in providing the best possible measure of potential risk to humans, no matter how elegant the study design or appropriate the animal model used. It is self-evident that, when appropriate safety/uncertainty factors are applied, risk assessments based on good quality human data cannot be improved upon by projections based on animal data. Thus developing and using human data is a critically important step in the process of risk assessment, significantly reducing its inherent uncertainty. The U.S. Interagency Staff Group on Carcinogens concurs with this view, stating that

"epidemiological investigations comprise one of the major strategies in creating the scientific base necessary for regulatory decision-making... [and] are useful in generating and refining hypotheses about potential cancer risk factors.... This...makes a strong argument for...inclusion of their results in regulatory decision-making, whenever relevant exposure has occurred in human populations" (1986a). "Even if an epidemiology investigation fails to demonstrate an increased incidence of carcinogenicity among exposed study members, upper and lower confidence limits on the risk measure used in the study can indicate a range of probable risk that could be incurred by a similarly composed segment (i.e., in terms of age, race, sex etc.) of the general population" (1986b).

U.S. EPA guidelines too are consistent with this approach. For example, at a recent workshop on cancer risk assessment guidelines (U.S. EPA, 1989), one of the major conclusions was that, where available, human epidemiology results should be given equal or greater weight than animal data. Furthermore, in "Guidelines For Carcinogen Risk Assessment," (U.S. EPA, 1986), the Agency states that "negative results from such [epidemiology] studies cannot prove the absence of carcinogenic action; however, negative results from a well-designed and well-conducted epidemiology study that contains usable exposure data can serve to define the upper limits of risk; these are useful if animal evidence indicates that the agent is potentially carcinogenic in humans."

The human exposure and epidemiology reports for aldrin/dieldrin represent a major strength of the overall data package. As pointed out above, the scope and duration of these studies of workers exposed to high concentrations of aldrin/dieldrin, together with information on individual exposure levels, increase confidence in their findings of no significant increase in frequency of any tumor types in humans.

Certain weaknesses which reduce the predictive value of this human exposure data should not be ignored, however, e.g.: (1) Many of the subjects in the epidemiological studies were simultaneously exposed to other toxicologically significant compounds, making attribution of any of any pathological findings to a specific chemical difficult. However, as there have been no significant findings to date, this problem has not been encountered. (2) A relatively small number of subjects were included in the epidemiology studies, limiting the statistical power of the data analyses. (3) Exposure levels and durations were variable among the subjects.

The appropriateness of the animal models used in toxicity testing protocols must also be carefully evaluated with respect to their applicability to the human species. The development of liver tumors in mice is a natural phenomenon, increasingly encountered as they age. Certain chemicals are known to promote the natural development of these tumors. The mechanism of this effect is not fully understood at present, and research in this area is currently very active. The relevance of the mouse liver tumor to other species is therefore unclear, controversial, and a significant source of uncertainty in cancer risk assessment. Some, including the U.S. EPA, consider that the occurrence of such tumors in mice must be considered to be predictive of human carcinogenicity; the CAG classification of aldrin/dieldrin as B2 reflects this position. Others, including WHO, IARC, and NTP, consider that since the propensity for spontaneous development of liver tumors is a murine peculiarity, tumorigenicity in this species should not form the sole basis for ranking a chemical which is not carcinogenic in other experimental animals (and, most importantly, humans) as a "probable" human carcinogen. U.S. EPA itself acknowledges that "There are widely diverging scientific views...about the validity of the mouse liver tumors as an indication of potential carcinogenicity in humans when such tumors occur in strains with high spontaneous background incidence and when they constitute the only tumor response to an agent" (U.S. EPA, 1986c).

The choices of which low-dose extrapolation model to use and of the animal data set to utilize in the model to derive estimates of upper bounds of risk are other substantive matters not currently settled. Different extrapolation models and data sets may lead to large differences in estimates of risk at low doses. The U.S. EPA states that "no single mathematical procedure is recognized as the most appropriate for low-dose extrapolation in carcinogenesis" (U.S. EPA, 1986), and "an established procedure does not yet exist for making "most likely" or "best" estimates of risk within the range of uncertainty defined by the upper and lower limit estimates" (U.S. EPA, 1986). The latter statement applies also to the linearized multistage model currently espoused by the Agency.

In view of the myriad uncertainties of interspecific extrapolation, the designated "upper-limit risk" should be accompanied, where appropriate, with explicit acknowledgment that the agent may not be a human carcinogen at all, and that there may be zero risk of cancer to humans due to exposure. Moreover, it should be made clear that there is currently no way to decide whether the upper-bound value for risk is more or less likely to be the true risk than the lower-bound value (zero). In the case of aldrin/dieldrin, it should be concluded that the true carcinogenic risk is as likely to be zero as to be any positive value whatsoever, whether 10^{-9}, 10^{-6} or 10^{-3}.

Models of carcinogenic risk are continually evolving. Models such as those of Moolgavkar and Venzon (1979), Moolgavkar and Knudson (1981), Sielken (1987) and Thorsland (1987) can incorporate information on cell turnover, providing estimates of risk which more satisfactorily fit the data. By taking alterations in cell dynamics into account, these models tend to reduce uncertainty in the extrapolation process, particularly in cases where there may be major qualitative and/or quantitative species differences (as in the case of aldrin/dieldrin).

In conclusion, it is clear that the mouse liver tumor issue is of critical importance in understanding the rational of U.S. EPA's CAG classification -- a point which the Agency itself acknowledges. The assumption that murine neoplasia predicts human tumors is a subject of intense scientific controversy at present; reference doses based on a different interpretation of the aldrin/dieldrin database have therefore been included in this document. In the case of aldrin/dieldrin, where data are available for exposed humans, the lack of an increase in human liver tumors should be taken into account. It is therefore important to provide the foregoing perspective to enable informed decision making about potential significant exposure levels associated various adverse health effects of these compounds.

REFERENCES

ATSM. 1985. Standard Practice for Conducting Bioconcentration Tests with Fishes and Saltwater Bivalve Mollusca. Designation E 1022-84, pages 590-62. In: 1985 Annual Book of ATSM Standards Volume 11.04. American Society for Testing and Materials, Philadelphia, Pennsylvania.

BRIGGS, C.G. 1981. Theoretical and Experimental Relationships between Soil Absorption, Octanol-Water Partition Coefficients, Water Solubility, Bioconcentration Factors and the Parachor. J. Agric. Food Chem. 29(3):1050-1059.

CHAWLA, R.P., K.L. KALRA and B.S. JOIA. 1981 Absorption of Residues of Soil Applied Aldrin and Heptachlor in Potatoes. Indian J. Ent., 43(3):266-271.

DAVIES, R.P. and A.J. DOBBS. 1984. The Prediction of Bioconcentration in Fish. Water Research, 18(10):1253-1262.

GEYER, H., G. POLITZKI and D. FREITAG. 1984. Prediction of Ecotoxicological Behavior of Chemicals: Relationship between n-Octanol/Water Partition Coefficient and Bioaccumulation of Organic Chemicals by Alga Chlorella. Chemosphere, 13(2):269-284.

HUDSON, R.H., R.K. TUCKER and M.A. HAEGALE. 1984. Handbook of Toxicity of Pesticides to Wildlife. Second Edition. United States Department of the Interior Fish and Wildlife Service. Resource Publication 153. Washington, D.C. 1984.

JAGER, K.W. 1970. Aldrin, Dieldrin, Endrin and Telodrin. Elservier Publishing Co., New York. 234 pages.

KADEG, R.D., S.P. PAVLOU and A.S. DUXBURY. 1986. Elaboration of Sediment Normalization Theory for Non-polar Hydrophobic Organic Chemicals. U.S. Environmental Protection Agency, Criteria and Standards Division, Washington D.C.

KENAGA, E.E. 1980. Correlation of Bioconcentration Factors of Chemicals in Aquatic and Terrestrial Organisms with their physical and Chemical Properties. Environ. Sci. Technol. 14(5):553-556.

KOHLI, J., S. ZARIF, I. WEISGERBER, W. KLEIN and F. KORTE. 1973. Fate of Aldrin-^{14}C in sugar beets and soil under outdoor conditions. J. Agr. Food Chem., 21(5):855-857.

LYMAN, W.J., W.F. REEHL and D.H. ROSENBLATT. 1982. Handbook of Chemical Property Estimation Methods: Environmental Behavior of Organic Compounds. McGraw-Hill Book Co., New York, NY.

MERCK INDEX. 1983. An encyclopedia of Chemicals, Drugs and Biologicals. Tenth Edition. Merck and Company, INc. Rathway, New Jersey.

NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH (NIOSH). 1978. Special Occupational Hazard Review for Aldrin/Dieldrin. Rockville Maryland. September 1978. USDHEH Publication No. 78-201.

NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH (NIOSH). 1982. Registry of Toxic Effects of CHemical Substances. Volumes I-III.U.S. Department of Health and Human Services, Cincinnati, OH. October 1983. Cincinnati, OH.

PAVLOU, S. P. 1980. Thermodynamic Aspects of Equilibrium Sorption of Persistent Organic Molecules at the Sediment-Seawater Interface: A Framework For Predicting Distributions in the Aquatic Environment. In: contaminants and sediments. volume 2. Baker, R.A. (Editor). Science Publishers, Inc. Ann Arbor, MI.

RAO, P.S.C. and J.M. DAVIDSON. 1983. Estimation of Pesticide Retention and transformation Parameters Required in Nonpoint Source Pollution Models. In: Overcash, M.R. and J.M. Davidson, editors Environmental Impact of Nonpoint Source Pollution. Ann Arbor Science Publishers, Inc. Ann Arbor, MI.

ROSENBLATT, D.H., T.A. MILLER, J.C. DACRE, I. MUUL and D.R. COGLEY. 1975. Problem Definition Studies on Potential Environmental Pollutants. II. Physical, Chemical, Toxicological, and Biological Properties of 16 Substances. Technical Report 7509. U.S. Army Medical Bioengineering Research and Development Laboratory, Fort Detrick MD.

TELEKAR, N.S., J.S. CHEN and H.T. KAO. 1983. Long-term persistence of selected insecticides in subtropical soil: Their absorption by crop plants. J. Econ. Entomol., 76(2):207-214.

U.S. ENVIRONMENTAL PROTECTION AGENCY (U.S. EPA). 1979. Water-Related environmental fate of 129 priority chemicals. Washington, D.C. December 1979. U.S. EPA 440/4-79-029.

U.S. ENVIRONMENTAL PROTECTION AGENCY (U. S. EPA). 1980. Ambient water quality criteria for aldrin/dieldrin. Office of water regulations and standards, criteria and standards division, Washington D.C., October 1980. U.S. EPA 440/5-80-019.

U.S. ENVIRONMENTAL PROTECTION AGENCY (U.S. EPA). 1985. Office of waste program enforcement. September 1985. Chemical,physical and biological properties of compounds present at hazardous waste sites. A final report prepared by Clement Associates, Inc., Arlington, VA.

U.S. ENVIRONMENTAL PROTECTION AGENCY (U.S. EPA). 1986. Superfund public health evaluation manual. Office of Emergency and Remedial Response. Washington, D.C. U.S. EPA 540/1-86/060.

U.S. ENVIRONMENTAL PROTECTION AGENCY (U.S. EPA). 1990. Integrated risk information system (IRIS). Access date: June 27, 1989. [Note: This is a computerized data base.]

VERSAR INC. 1984. Draft final report: Chemical and toxicological review of priority contaminants in Nearshore Tideflats and Deepwater of Commencement Bay, Washington. Versar Inc. Springfield, VA.

VERSCHUEREN, K. 1977. Handbook of environmental data on organic chemicals. Van Norstrand Reinhold Co., New York. 659 pages.

WEAST, R.E., ed. 1981. Handbook of Chemistry and Physics. 62nd ed. CRC Press, Cleveland, Ohio. 2332 pages.

ADDITIONAL REFERENCES

Adamson, R. H. and Sieber, S. M., "Chemical carcinogenesis studies in nonhuman primates;" In: Organ and species specificity chemical carcinogenesis, Langenbach, *et al.*, Eds., Plenum Publ. Corp. (1983).

Ahmed, F. E., Hart, B. W. and Lewis, N. J., "Pesticide-induced DNA damage and its repair in cultured human cells," Mutat. Res., 42: 161-174 (1977a).

Ahmed, F. E., Lewis, N. J. and Hart, B. W., "Pesticide-induced ouabain restant mutants in Chinese hamster V79 cells," Chem.-Biol. Interactions, 9: 369-374 (1977b).

Akkermans, L. M. A., "Mode of action of dieldrin. An electrophysiological investigation," Thesis, Rijksuniversiteit Utrecht, The Netherlands (1974).

Akkermans, L. M. A., van den Bercken, J. and Versluys-Helder, M., "Excitatory and depressant effects of dieldrin and aldrin-transdiol in the spical cord of the toad (Xenopus laevis)," Europ. J. Pharmacol., 34: 262-269 (1975).

Anderson, H. H., "Class B determinations on insecticide preparations," San Francisco, University of California, (1951-1954).

Anderson, J. P. E., Lichtenstein, E. P. and Whittingham, W. F., "Effect of Mucor alternans on the persistence of DDT and dieldrin in culture and in soil," J. Economic Entomol., 63(5): 1595-1599 (1970).

Ashwood-Smith. M. J., "The genetic toxicology of aldrin and dieldrin," Mutation Res., 86: 137-154 (1981)

Avar, P. and Czegledi-Janko, G., "Occupational exposure to aldrin: clinical and laboratory findings," Brit. J. Ind. Med., 27: 279-282 (1970).

Baker, A. H., Whitney, G. F. H. and Worden, A. N., "The toxic hazard associated with continuous-flow heat-volatilized insecticidal and acaricidal aerosols," Lab. Practice, 8: 3-10 (1959).

Borgmann, A. R., Kitselman, C. H., Dahm, P. A. and Pankaskie, J. E., "Toxicological studies of aldrin on small laboratory animals," Cincinnati, Kettering Laboratory, (1952).

Bragt, P. C., Schuurbiers, C. J., Hollander, J. C. Th., Schulting, F. L. and Wolthuis, O. L., "Retention of inhaled aldrin in man," Rijswijk (The Netherlands), Medical Biological Laboratory TNO, (1984).

Brown, V. K. H., C. G. Hunter and A. Richardson, "Preliminary studies on the acute and subacute toxicities of a photoisomerization product of HEOD," Fd. Cosmet. Toxicol., 5: 771-779 (1964).

Cabral, J. R. P., *et al.*, "A carcinogenicity study of the pesticide dieldrin in hamsters," Cancer Letters, 6: 241-246 (1979).

Chernoff, N., Kavlock, R. J., Kathrein, J. R., Dunn, J. M. and Haseman, J. K., "Prenatal effects of dieldrin and photodieldrin in mice and rats," Toxicol. Appl. Pharmacol., 31: 302-308 (1975).

Costella, J. C. and B. B. Virgo, "Is dieldrin-induced cogenital inviability mediated by central nervous system stimulation or altered carbohydrate metabolism?," Can. J. Physiol. Pharmacol., 58: 633-637 (1980).

Coulston, F., Abraham, R. and Mankes, R., "Reproductive study in female rats given dieldrin, alcohol or aspirin orally," Albany, Albany Medical College of Union University, Institute of Comparative and Human toxicology, (1980).

Curley, A., Copeland, M. F. and Kimbrough, R. D., "Chlorinated hydrocarbon insecticides in organs of stillborn and blood of newborn babies," Arch. Environ. Health, 19: 628-632 (1969).

Dale, W. E., Curley, A. and Cueto, C., "Hexane extractable chlorinated insecticide in human blood," Life Sciences 5: 47-54 (1966).

Davis, K. J. and Fitzhugh, O. G., "Tumorigenic potential of aldrin and dieldrin for mice," Toxicol. Appl. Pharmacol., 4: 187-189 (1962).

Dean, B. J., Doak, S. M. A. and Sommerville, H., "Potential mutagenicity of dieldrin (HEOD) in mammals," Food Cosmet. Toxicol., 13(3): 317-323 (1975).

DeFlora, S., Zannacchi, P., Camoirano, A., Bennicelli, C. and Badolati, C., "Genotoxic activity and potency of 135 compounds in the Ames reversion test and in a bacterial DNA-repair test," Mutat. Res. 133: 161-198 (1984).

Deichmann, W. B., MacDonald, W. E., Radomski, J., Blum, E. B., Belivaqua, M., Keplinger, M. L. and Balkus, M., "Tumorigenicity of aldrin, dieldrin and endrin in the albino rat," Industr. Surg. 39: 426-434 (1970).

Deichmann, W. B., MacDonald, W. E., Beasley, A. G. and Cubit, D., "Subnormal reproduction in beagle dogs induced by DDT and aldrin," Ind. Med. Surg., 40: 10-20 (1971).

Deichmann, W. B., MacDonald, W. E. and Lu, F., "Effects of chronic aldrin feeding in two strains of female rats, and a discussion of the risks of carcinogens in man," In: Deichmann, W. B. (ed.), Toxicology and Occupational Medicine, Amsterdam, Elsevier/North Holland, p 407-413 (1979).

de Jong, G., "Long-term health effects of aldrin and dieldrin. A study of exposure, results of health surveillance and mortality experience of workers engaged in the manufacturing and formulation of aldrin and dieldrin." The Hague, The Netherlands: Shell International Petroleum Maatschappij B. V. (1990).

D'Ercole, A. J., Arthur, R. D., Cain,J. D. and Barrentine, B. F., "Insecticide exposure of mothers and newborns in a rural agricultural area," Pediatrics, 57(6): 869-874 (1976).

Ditraglia, D., Brown, D. P., Namekata, T. and Iverson, N., "Mortality studies of workers employed at organochlorine pesticide manufacturing plants," Scand. J. Work. Environ. Health, 7 (suppl. 4):140-146 (1981).

Diwan, B. A., Rice, J. M. and Ward, J. M., "Tumor-promoting activity of benzodiazepine tranquilizers, diazepam and oxazepam, in mouse liver," Carcinogenesis, 7(5): 789-794 (1986).

Dix, K. M. and Wilson, A. B., "Toxicity studies with dieldrin (HEOD). Teratogenic studies in rabbits given HEOD and thalidomide orally," Sittingbourne, Shell Research, TLGR.0051071 (1971).

Dix, K. M., van der Pauw, C. L. and McCarthy, W. V., "Toxicity studies with dieldrin: Teratological studies in mice dosed with HEOD," Teratology 16: 57-62 (1978).

Dix, K. M., "An investigation into some aspects of the pathogenesis of rodent liver cell neoplasms," Thesis for Doctor of Philosophy degree, University of Surry, Guildford (1981).

Eisenlord, G., Loquvam, G. S. and Nemenzo, J. " Results of reproduction study of rats fed diets containing dieldrin over three generations," San Francisco, The Hine Laboratories, Report No. 4,(1967).

Environmental Protection Agency (U.S. EPA), "Guidelines for carcinogen risk assessment," 51 Fed. Reg. 33997-33998, 24 Sep (1986a).

Environmental Protection Agency (U.S. EPA), "Guidelines for carcinogen risk assessment," 51 Fed. Reg. 33997, 24 Sep (1986b).

Environmental Protection Agency (U.S. EPA), "Guidelines for carcinogen risk assessment," 51 Fed. Reg. 33992-33995, 24 Sep (1986c).

Epstein, S. S., Arnold, E., Andrea, J., Bass, W., and Bishop, Y., "Detection of chemical mutagens by the dominant lethal assay in the mouse," Toxicol. Appl. Pharmacol., 23: 288-325 (1972).

Epstein, S. S., "The carcinogenicity of Dieldrin. Part I," Sci. Total Environ., 4:1-52 (1975).

FAO/WHO, "Joint meeting on pesticide residues in food," 1977 Evaluations, Rome, FAO, p 7 (1978).

Fitzhugh, O. G., Nelson, A. A. and Quaife, L., "Chronic oral toxicity of aldrin and dieldrin in rats and dogs," Fd. Cosmet. Toxicol., 2:551-561 (1964).

Fries, G. F., "Degradation of chlorinated hydrocarbons under anaerobic conditions," Advances in Chemistry Series No. 3, S. D. Faust (ed), Am. Chemical Soc., Wash., D. C., p 256-269 (1972).

Garrettson, L. K. and Curley, A., Dieldrin: studies in a poisoned child," Arch. Environ. Health, 19: 814-822 (1969).

Glatt, H., Jung, R. and Oesch, F., "Bacterial mutagenicity investigation of epoxides, drugs and pesticides," Mutat. Res., 11: 98-118 (1983).

Good, E. E. and Ware, G. W., "Effects of insecticides on reproduction in the laboratory mouse. IV. Endrin and dieldrin," Toxicol. Appl. Pharmacol., 14: 201-203 (1969).

Gupta, P. C., Neurotoxicity of chronic chlorinated hydrocarbon insecticide poisoning - A clinical and electroencephalographic study in man," Indian J. Med. Res., 63: 601-606 (1975).

Harr, J. R., Claeys, R. R., Bone, J. F. and McCorcle, T. W., "Dieldrin toxicosis: rat reproduction," Am. J. Vet. Res., 31: 181-189 (1970).

Haworth, S., Lawloe, T., Mortlemans, J., Speck, W. and Zeigler, E., "Salmonella mutagenicity test results for 250 chemicals," Environ. Mutagen 5: 3-142 (1983).

Hayes, W. J., Jr., and Curley, A., "Storage and excretion of dieldrin and related compounds: Effects of occupational exposure," Arch. Environ. Health, 16: 155-162 (1968).

Hazardous Substances Data Bank, File on aldrin, National Library of Medicine On-Line Database (1990).

Hoogendam, I., Versteeg, J. P. J. and de Vleiger, M., "Electroencephalograms in insecticide toxicity," Arch. Environ. Health, 4: 86-94 (1962).

Hoogendam, I., Versteeg, J. P. J. and de Vleiger, M. , "Nine years' toxicity control in ecticide plants," Arch. Environ. Health, 10: 441-448 (1965).

Hunt, P. F., Stevenson, D. E., Thorpe, E and Walker, A. I. T., "Mouse Data" (Letter to the editors), Food & Cosmetics Toxicol., 13: 597 (1975).

Hunter, C. G. and Robinson, J., "Pharmacodynamics of dieldrin (HEOD): I. Ingestion by human subjects for 18 months," Arch. Environ. Health, 15: 614-626 (1967).

Hunter, C. G., Robinson, J. and Roberts, M., "Pharmacodynamics of dieldrin (HEOD): II. Ingestion by human subjects for 18 to 24 months, and post-exposure for 8 months," Arch. Environ. Health, 18: 12-21 (1969).

Hunter, J., Maxwell, J. D., Carrella, M., Stewart, D. A. and Williams, R., "Urinary D-glucaric acid excretion as a test for hepatic enzyme induction in man," The Lancet, 20 Mar, p 572-575 (1971).

International Agency for Research on Cancer (IARC) monographs on the evaluation of the carcinogenic risks of chemicals to humans; Chemicals, industrial processes and

industries associated with cancer in humans, IARC Monographs, Supplement 4, Oct. (1982).

International Agency for Research on Cancer (IARC) monographs on the evaluation of the carcinogenic risks of chemicals to humans; Chemicals, industrial processes and industries associated with cancer in humans, IARC Monographs, Supplement 7, Mar. (1987).

Jager, K. W., "Aldrin, dieldrin, endrin and telodrin: An epidemiological and toxicological study of long-term occupational exposure," Elsevier Publ. Co., New York, Amsterdam, (1970).

Joy, R. M., "The alteration by dieldrin of cortical excitability by sensory stimuli," Toxicol. Appl. Pharmacol., 38: 357-368 (1976).

Kaminski, N. E., Roberts, J. F. and Guthrie, E. F., "The effects of DDT and dieldrin on rat peritoneal macrophages," Pestic. Biochem. Physiol. 17: 191 (1982).

Kazantzis, G., McLaughlin, A. I. G. and Prior, P. F., "Poisoning in industrial workers by the insecticide aldrin," Brit. J. Ind. Med., 21: 46-51 (1964).

Kitselman, C. H., "Long term studies on dogs fed aldrin and dieldrin in sublithal dosages, with reference to the histopathological findings and reproduction," J. Am. Vet. Med. Assoc., 123: 28-30 (1953).

Klaunig, J. E., Goldblatt, P. J., Hinton, D. E., Lipsky, M. M. and Trump, B. F., "Carcinogen-induced unscheduled DNA synthesis in mouse hepatocytes," Toxicol. Pathol., 12: 119-125 (1984).

Krzystyniak, K., Flipo, D., Mansour, S. and Fournier, M., "Suppression of avidin processing and presentation by mouse macrophages after sublethal exposure to dieldrin," Immunopharmacol., 18: 157-166 (1989).

Kurata, M., Hirose, K. and Umeda, M.," Inhibition of metabolic cooperation in Chinese hamster cells by organochloride pesticides," Gann., 73: 217-221 (1982).

Macdonald, R. L. M., "Toxicology of sprays: The 4h acute inhalation toxicity of aqueous sprays prepared from aldrin 48% (w/v) EC," Sittingbourne, Shell Research, SBGR.82.036 (1982).

Majumdar, S. K., Kopelman, H. A. and Schnitman, M. J., "Dieldrin induced chromosome damage in mouse bone marrow and WI-38 human lung cells," J. Hered. 67: 303-307 (1976).

Majumdar, S. K., Maharam, L. G. and Viglianti, G. A., "Mutagenicity of dieldrin in the Salmonella-microsome test," J. Hered. 68: 184-185 (1977).

Marshall, T. C., Dorough, H. W. and Swim, H. E., "Screening of pesticides for mutagenic potential using Salmonella typhimurium mutants," J. Agric. Food Chem., 24: 560-563 (1976).

Matsumura, F. and Boush, G. M., "Dieldrin: degradation by soil microorganisms," Science, 156: 959-961 (1967).

Matsumura, F. and Boush, G. M., "Degradation of insecticides by a soil fungus, Trichoderma viride," J. Economic Entomol., 61: 610-612 (1968).

Matsumura, F., Boush, G. M. and Tai, A., "Breakdown of dieldrin in soil by a microorganism," Nature (London), 219: 965-967 (1968).

Matsumura, F., "Metabolism of insecticides in microorganisms and insects," Environ. Qual. Safety, 1:96-106 (1972).

Meierhenry, E. F., Ruebner, B. H., Gershwin, M. E., Hsieh, L. S. and French, S. W., "Mallory body formation in hepatic nodules of mice ingesting dieldrin," Lab. Invest., 44(4): 392-396 (1981).

Moolgavkar, S. H. and Venzon, D. J., "Two-event models for carcinogenesis: Incidence curves for childhood and adult tumors," Math. Biosci., 47: 55-77 (1979).

Moolgavkar, S. H. and Knudson, A. G., Jr., "Mutation and cancer: A model for human carcinogenesis," JNCI, 66: 1037-1052 (1981).

Morgan, D. P. and Roan, C. C., "Liver function in workers havinghigh tissue stores of chlorinated hydrocarbon pesticides," Arch. Environ. Health, 29: 14-17 (1974).

Moriarty, F., "Exposure and residues," Chapter 2 in "Organochlorine insecticides: persistant organic pollutants," Academic Press, New York, NY, p 29-72 (1975).

NCI (National Cancer Institute), "Bioassay of photo-dieldrin for possible carcinogenicity," CAS No. 13366-73-9; NCI-CG-TR.17, Technical Report Series No. 17. DHEW Publ. \no. (NIH) 77-817 (1977).

NCI (National Cancer Institute), "Bioassay of aldrin and dieldrin for possible carcinogenicity," CAS No's 309-00-2 and 60-571; NCI-CG-TR-21; Technical Report Series No. 21. DHEW Publ. No. (NIH) 78-821 (1978a).

NCI (National Cancer Institute), "Bioassay of dieldrin for possible carcinogenicity," CAS No. 60-57-1; NCI-CG-TR-22; Technical Report Series No. 22. DHEW Publ. No. (NIH) 78-822 (1978b).

Newberne, P. M., "Assessment of the hepatotoxic and hepatocarcinogenic potential of chemicals," Inst. Natnl. Sante Rech. Med. (Colloq.), 132, Iss Hepatotoxic. Med.: 75-110 (1986).

NIOSH (National Institute for Occupational Safety and Health), "Special Occupational Hazard Review: Aldrin/Dieldrin," U.S. Dept. Health, Education and Welfare, Public Health Service, Center for Disease Control, Division of Criteria Documentation and Standards Development, Rockville, MD, NIOSH Publication No. 78-201, September (1978).

O'Leary, J. A., Edmundson, J. E. and Reich, C. A., "Transplacental passage of pesticides," Am. J. Obstet. Gynecol., 107: 65-68 (1970).

Ottevanger, C. F. and van Sittert, N. J., "Relation between anti-12-hydroxy endrin excretion and enzyme induction in workers involved in the manufacture of endrin," in: Strik, J.J.T.W.A. and Koeman, J. H., (Eds), Chemical porphyria in man, pp. 123-129, Elsevier/North Holland Biomedical Press, (1979).

Ottolenghi, A. D., Haseman, J. K. and Suggs, F., "Teratogenic effects of aldrin, dieldrin and endrin in hamsters and mice," Teratology, 9: 11-16 (1974).

Polishuk, Z. W., Wassermann, D., Wassermann, M., Gucos, S. and Ron, M., "Pesticides in people: Organochlorine compounds in mother and fetus during labor," Environ. Res., 13: 278-284 (1977).

Probst, G. S., McMahon, R. E., Hill, L. E., Thompson, C. Z., Epp, J. K. and Neal, S. B., "Chemically-induced unscheduled DNA synthesis in primary rat hepatocyte cultures: A comparison with bacterial mutagencicty using 218 compounds," Environ. Mut., 3: 11-32 (1981).

Ramel, C., Alekperov, U. K., Ames, B. N., Kada, T. and Wattenberg, L. W., "Inhibitors of mutagenesis and their relevance to carcinogenesis," International Commission for Protection Against Environmental Mutagens and Carcinogens (ICPEMC) publication No. 12, Mutation Research, 168: 47-65 (1986).

Ribbens, P. H., "Mortality study of industrial workers exposed to aldrin and dieldrin and endrin," In. Arch. Occup. Environ. Health, 56:75-79 (1985).

Ruch, R. J. and Klaunig, J. E., "Effects of tumor promoters, genotoxic carcinogens and hepatocytotoxins on mouse hapatocyte intercellular communication," Cell Biol. and Toxicol., 2(4): 469-483 (1986).

Sandifer, S. H., Cupp, C. M., Wilkins, R. T., Loadholt, B. and Schuman, S. H., "A case control study of persons with elevated blood levels of dieldrin," Arch. Environ. Contamin. Toxicol., 10: 34-45 (1981).

Saxena, M. C., Seth, T. D., and Mahajan, P., "Organochlorine pesticides in human placenta and accompanying fluid," Int. J. Environ. Anal. Chem., 7(3): 245-252 (1980).

Sielken, R. L., "Combining physiology, carcinogenic mechanism and interindividual variation and cancer dose-response extrapolations," Society For Risk Analysis Annual Meeting, Nov. 1-4 (1987).

Sielken, R. L., "Information-analysis-based quatitative risk characterization. Combining information on human exposures with information on health effects from animal experimental data and human data including epidemiological data: an illustration based on dieldrin." Bryan, Texas: Sielken, Inc. (1990).

Spiotta, E. J., "Aldrin poisoning in man. Report of a case," Arch. Ind. Hyg. Occup. Med., 4: 560-566 (1951).

Stevenson, D. E., and Walker, A. I. T., "Hepatic lesions produced by dieldrin and other hepatic enzyme inducing compounds," J. Europ. Toxicol., 2:83-84 (1969).

Stevenson, D. E., Thorpe, E., Hunt, P. F. and Walker, A. I. T., "The toxic effects of dieldrin in rats: A re-evaluation of data obtained in a two-year feeding study," Toxicol. Appl. Pharmacol., 36: 247-254 (1976).

Taylor, J. R. and Calabrese, V. P., "Organochlorine and Other Insecticides," Handb. Clin. Neurol., 36: 391-455 (1979).

Tennekes, H. A., Elder, L. and Kunz, H. W., "Dose-response analysis of the enhancement of liver tumour formation in CF-1 mice by dieldrin," Carcinogenesis, 3(8): 941-945 (1982).

Thorpe, E. and Walker, A. I. T., "Toxicology of dieldrin (HEOD): II. Comparative long-term oral toxicity studies in mice with dieldrin, DDT, phenobarbitone, beta-BHC and alpha-BHC," Fd. Cosmet. Toxicol., 11: 433-442 (1973).

Thorslund, T. W., Brown, C. C. and Charnley, G., "Biologically motivated cancer risk models," Risk Analysis, 7(1): 109-119 (1987).

Treon, J. F. and Cleveland, F. P., "Toxicity of certain chlorinated hydrocarbon insecticides for laboratory animals, with special reference to aldrin and dieldrin," Agric. Fd. Chem., 3: 402-408 (1955).

Trosko, J. E., Jone, C. and Chang, C. C., "Inhibition of gap junctional-mediated intercellular communication in vitro by aldrin, dieldrin and toxaphene; a possible cellular mechanism for their tumor promoting and neurotoxic effects," Mol Toxicol., 1: 83-93 (1987).

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA), Guidelines for Carciongen Risk Assessment," Federal Register, 51(185): 3395-6, 24 Sept. (1986).

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA), "Cancer Risk Assessment Guidelines - Human Evidence Workshop," Washington, D. C., 26-27 June (1989).

U. S. Interagency Staff Group on Carcinogens, "Chemical carcinogens: A review of the science and its associated principles," Environ. Health Persp., 67: 201-282 (1986a).

U. S. Interagency Staff Group on Carcinogens, "Chemical carcinogens: A review of the science and its associated principles," Environ. Health Persp., 67: 254 (1986b).

van Genderen, H., "Dieldrin, a problem insecticide," Versl. Gewone Vergad. Afd. Natuurkd., K. Ned. Akad. Wet., 88(3): 24-32 (1979).

van Raalte, H. G. S., "Human experience with dieldrin in perspective," Ecotox. Environ. Safety, 1: 203-210 (1977).

van Sittert, N. J. and de Jong, G., "Evaluation of liver function with biochemical tests of operators engaged in aldrin and dieldrin manufacturing," (prepared for U.S. Environmental Protection Agency registration standard on aldrin), Scallop Corporation, N. Y., N. Y., 27 May (1987).

Versteeg, J. P. J. and Jager, K. W., "Long-term occupational exposure to aldrin, dieldrin, endrin and telodrin," Brit. J. Industr. Med., 30: 201-202 (1973).

Virgo, B. B. and Bellward, G. D., "Effects of dietary dieldrin on reproduction in the Swiss-Vancouver (SWV) mouse," Environ. Physiol. Biochem., 5: 440-450 (1975).

Virgo, B. B. and Bellward, G. D., "Effects of dietary dieldrin on offspring viability, maternal behaviour and milk production in the mouse," Res. Comm. Chem. Pathol. Pharmacol., 17(3): 399-409 (1977).

Wade, M. H., Trosko, J. E. and Schindler, M., "A fluorescence photobleaching assay of gap junction mediated communication between human cells," Science, 232: 525-528 (1986).

Walker, A. I. T., Stevenson, D. E., Robinson, J., Thorpe, E. and Roberts, M., "The toxicology and pharmacokinetics of dieldrin (HEOD): Two year oral exposure of rats and dogs," Toxicol. Appl. Pharmacol., 15: 345-373 (1969).

Walker, A. I. T., Thorpe, E., and Stevenson, D. E.," The toxicology of dieldrin (HEOD). I. Long-term oral toxicity studies in mice," Fd. Cosmet. Toxicol., 11: 415-432 (1972).

Warnick, S. L. and Carter, J. E., "Some findings in a study of workers, occupationally exposed to pesticides," Arch. Environ. Health, 25: 265-270 (1972).

Wedemeyer, G., "Partial hydrolysis of dieldrin by Aerobacter aerogenes," Appl. Microbiol., 16: 661-662 (1968).

World Health Organization (WHO), Draft final (but still unedited) summary, evaluation, conclusions and recommendations of the Task Group on Aldrin and Dieldrin, International Programme on Chemical Safety, Division of Environmental Health, July, 1987.

Wright, A. S., Potter, D., Wooder, M. F., Donninger, C. and Greenland, R. D., "The effects of dieldrin on the subcellular structure and function of mammalian liver cells," Fd. Cosmet. Toxicol., 10: 311-332 (1972).

Wright, A. S., Akintonwa, D. A. A. and Wooder, M. F., " Studies on the interaction on dieldrin with mammalian liver cells at the subcellular level," Ecotox. Environ. Safety, 1: 7-16 (1977).

Wright, A. S., Donninger, C., Greenland, R. D., Stemmer, K. L. and Zavon, M. R., "The effects of prolonged ingestion of dieldrin on the livers of male Rhesus monkeys," Ecotox. Environ. Safety, 1: 477-502 (1978).

ARSENIC

Summary

Arsenic is a metalloid that is present in the environment as a constituent of organic and inorganic compounds. Average arsenic concentrations in well water are generally less than 20 micrograms/liter and the average concentration of arsenic in U.S. drinking water is 2 micrograms/liter. Over 90% of all surface waters contain 10 micrograms/liter or less. Average 24 hour ambient air arsenic levels range from 2.6 to 10.9 ng/m^3. Natural arsenic content in virgin soils varies between 0.1 and 80 ppm. Arsenic levels in food, except fish, rang from 0.01 to 0.04 ppm. Finfish and shellfish are reported to contain an average of 0.07 to 1.47 ppm. Typical values for human exposure due to background are 0.06 micrograms from air, 5 ug from water and 21 ug from food. (ATSDR, 1988) EPA (1988) quotes FDA (1985) reporting that arsenic intake in the U.S. averages 46 ug arsenic/day. Arsenic occurs in a number of valence states. Arsenic is generally rather mobile in the natural environment, with the degree of mobility dependent on its chemical form and the properties of the surrounding media. Arsenic is a human carcinogen; it causes skin tumors when it is ingested and lung tumors when it is inhaled. The arsenic related skin tumors are similar to sunlight induced tumors except they tend to occur on the palms of the hands and the bottom of the feet. Sunlight related skin cancers occur in 500,000 people each year in the U.S. Arsenic compounds are teratogenic and cause adverse reproductive effects in animals. Chronic exposure to arsenic is associated with polyneuropathy (disorders of the nervous system) and skin lesions. It is acutely toxic to some early life stages of aquatic organisms at levels as low as 40 ug/liter.

Arsenic can be found in the environment in any of four valence states (-3, 0, +3, and +5) depending on the pH, Eh, and other factors. It can exist as either inorganic or organic compounds and often will change forms as its moves through the various media. The chemical and physical properties depend on the state of the

metalloid. Only the properties of metallic arsenic are presented below; properties of other arsenic compounds are often quite different

CAS Number:	7440-38-2
Chemical Formula:	As
IUPAC Name:	Arsenic

Chemical and Physical Properties

Atomic Weight:	74.91
Boiling Point:	613° C
Melting Point:	817° C
Specific Gravity:	5.72 at 20° C
Solubility in Water:	Insoluble; some salts are soluble

Transport and Fate

In the natural environment arsenic has four different oxidation states; chemical speciation is important in determining arsenic's distribution and mobility. Interconversions of the +3 and +5 states as well as organic complexation do occur and can be mediated by microorganisms. Arsenic is generally quite mobile in the environment and is mainly transported by water (WHO 1981). In oxygenated water, arsenic usually occurs as arsenate, but under reducing conditions, (i.e., deep well waters) arsenite predominates. In the aquatic environment, volatilization is important when biological activity or highly reducing conditions produce arsine or methyl-arsenic. Sedimentation of arsenic in association with iron and aluminum does occur frequently (WHO 1981).

In oxygenated soil, inorganic arsenic is prevalent in the pentavalent (+5) form. Under reducing conditions, the trivalent form predominates (WHO 1981).

Leaching of arsenates and arsenites occurs slowly due to binding with hydrous oxides of iron and aluminum. Biomethylation in soil does occur and may be associated with the release of methylarsines into the air (WHO 1981). Plant uptake of arsenic from treated soils can occur, however, accumulation is not excessive.

Freshwater residue data for arsenic (organic and inorganic) indicate that arsenic is not bioconcentrated to a high degree but that lower forms of aquatic life may accumulate higher residues than fish (USEPA 1984a, 1986a).

Health Effects

Arsenic may be an essential nutrient in humans and certain animal species. The animal data suggests small amounts of arsenic are required. The normal human daily intake of arsenic of 17 to 40 micrograms per day is expected to meet the normal human daily requirement. (EPA, 1988) However, arsenic has been implicated in the production of skin cancer in humans. There is also extensive evidence that inhalation of arsenic compounds causes lung cancer in occupationally exposed workers. Arsenic compounds also cause noncancerous (possibly precancerous) skin changes in exposed individuals. The pathologic hallmark of chronic arsenic exposures is hyperpigmentation, which is not considered to be a malignant neoplasm or a precursor to malignancy. (EPA, 1988) There has not been consistent demonstration of arsenic carcinogenicity in test animals for various chemical forms administered by different routes to several species. There are some data to indicate that arsenic may produce animal tumors if retention time in the lung can be increased. (IRIS, 1989).

EPA and the International Agency for Research on Cancer (IARC) have established that sufficient evidence exists to classify arsenic as a human carcinogen (USEPA 1984b); it is therefore classified as a Group A carcinogen (i.e. , human carcinogen) based upon evidence of human carcinogenicity through inhalation and ingestion exposure. Arsenic compounds have been observed to cause chromosome damage in

animals. Humans exposed to arsenic compounds have been reported to have an elevated incidence of chromosome aberrations.

Arsenic compounds have been reported to be teratogenic, fetotoxic, and embryotoxic in several animal species, and an increased incidence of multiple malformations among children born to women occupationally exposed to arsenic has been reported. Several cases of progressive polyneuropathy involving motor and sensory nerves and particularly affecting the extremities and myelinated long-axon neurons have been reported in individuals occupationally exposed to inorganic arsenic. Polyneuropathies have also been reported following the ingestion of arsenic-contaminated foods.

Toxicity to Wildlife and Domestic Animals

Various inorganic forms of arsenic appear to have similar levels of toxicity. Inorganic arsenic appears to be more toxic than organic forms. Acute toxicity to adult freshwater animals occurs at levels of arsenic trioxide as low as 812 ug/liter and at levels of as low as 40 ug/liter in early life stages of aquatic organisms. Acute toxicity to saltwater fish occurs at levels around 15 mg/liter, while some invertebrates are affected at much lower levels (508 ug/liter). Arsenic toxicity does not appear to increase greatly with chronic exposure, and it does not seem that arsenic is bioconcentrated to a great degree.

Arsenic poisoning is an uncommon but not a rare toxic syndrome among domestic animals. Arsenic causes hyperemia (site specific congestion) and edema (swelling) of the gastrointestinal tract, hemorrhage of the cardiac serosal surfaces and peritoneum, and pulmonary congestion and edema. It may also cause liver necrosis. Information on arsenic toxicity to terrestrial wildlife was not reported in the literature reviewed.

Regulations and Standards

Ambient Water Quality Criteria (USEPA 1986a):

Aquatic Life (Freshwater)

Acute toxicity (As^{+3}): 360 ug/liter

Chronic toxicity (As^{+3}): 190 ug/liter

Aquatic Life (Saltwater)

Acute toxicity (As^{+3}): 69 ug/liter

Chronic toxicity (As^{+3}): 36 ug/liter

Human Health

Due to the carcinogenicity of arsenic the ambient water criterion is set at zero. However, estimates of the carcinogenic risks from the ingestion of contaminated water and contaminated aquatic organisms are:

Risk	Concentration
10^{-5}	22 ng/liter
10^{-6}	2.2 ng/liter

CAG Potency Slope for Oral Exposure (USEPA 1986b): 1.5 (mg/kg/day)-1

CAG Potency Slope for Inhalation Exposure (USEPA 1989): 50 (mg/kg/day)-1

National Primary Drinking Water Standard: 50 ug/liter

The risk associated with the drinking water standard using the CAG oral potency slope of 1.5 is found by multiplying the daily intake associated with 100 micrograms (0.1 mg total in 2 L of water case) and dividing by 70 kilograms for a calculated risk of 2 x 10-3, or 1 in 500 (rounded off).

The calculated skin cancer risk associated with the average U.S. dietary intake of 46 micrograms/day is 1.5 x 6.5 x 10-4 = 9.7 x 10-4 or about 1 in 1000.

NIOSH Recommended Standard (air): Ceiling Level : 2 ug/m3
OSHA Standard (air) TWA[1/]: 500 ug/m3 (organic arsenic compounds)
ACGIH Threshold Limit Value: 200 ug/m3 (arsenic and soluble compounds)
1/ Time Weighted Average.

D_T Value

The D_T value is defined as that contaminant intake rate (mg/kg/day) that should not induce an adverse effect to human health or should not pose a risk of cancer occurrence greater than a predetermined risk level.

For carcinogens such as arsenic, the D_T value is based on the USEPA Cancer Assessment Group's cancer potency slopes. The potency slopes are intended to be a plausible upper bound of the potency of a carcinogen in inducing cancer at low doses. The cancer potency slopes have been estimated for oral exposure routes and for inhalation exposure for arsenic.

Calculation of a D_T using a cancer potency slope requires selection of an acceptable cancer risk level. A range of risk levels from 10^{-4} to 10^{-6} is considered for all carcinogens; therefore, a range of D_T values is presented. Derivation of the D_T values for arsenic follows. The potency slope used is 1.75 /mg/kg/day, which corresponds to the EPA's proposed unit risk of 5.5 /ug/L

$$D_T = \frac{\text{Risk Level}}{\text{Potency Slope (mg/kg/day)-1}}$$

$$= \frac{1 \times 10\text{-}4}{1.75 \text{ (mg/kg/day)-1}}$$

$$= 5.7 \times 10^{-5} \text{ mg/kg/day}$$

The range of D_T values for arsenic is presented below:

Risk Level	Oral D_T (mg/kg/day)	Inhalation D_T (mg/kg/day)
10^{-4}	5.7×10^{-5}	2.0×10^{-6}
10^{-5}	5.7×10^{-6}	2.0×10^{-7}
10^{-6}	5.7×10^{-7}	2.0×10^{-8}

STRENGTHS AND WEAKNESSES IN THE TOXICITY AND ONCOGENICITY OF ARSENIC FOR CONSIDERATION BY THE RISK MANAGER.

The risk assessment Forum in the Special Report on Ingested Inorganic Arsenic concluded that the uncertainties which are currently unresolvable on a scientific basis are best accounted for in the risk management portion of the decision-making process. Specifically, on a case-specific basis, the Council recommends that risk managers reach their judgments in light of the knowledge that:

1. Ingested inorganic arsenic is a class A carcinogen resulting in an increased incidence of skin cancers.

2. Only a fraction of the arsenic-induced skin cancers are fatal.

3. The non-fatal skin cancers remain of some concern.

4. The dose-response curve for the skin cancers may be sublinear, in which case the cancer potency (5 E-5 per microgram/L of water) in this report will overestimate the risks.

5. Arsenic may cause cancer in internal organs.

6. Arsenic is a possible but not proven nutritional requirement in animals. There are no direct data on the essentiality of arsenic in humans.

The major study supporting the cancer potency value is based on studies of Taiwanese populations drinking well water containing arsenic from early 1900's to mid 1960's. Apparently the water also was used for vegetable growing and fish farming, but the risk potency is based only on the drinking water intake (effect is to overestimate potency). The use of the water for fish farming may be important since fish accumulate more arsenic than other food sources (the potential importance is that arsenic exposure would be higher in the Taiwanese eating fish and the risk based only on per unit arsenic in drinking water would overestimate the actual risk since arsenic exposure was underestimated.)

In the early 1960's the water was reported to contain from 0.001 to 1.82 ppm arsenic. In 1983 the water was also reported to contain bacteria and ergot alkaloids, the later may be important since the incidence of the disease blackfoot appears to be higher in this arsenic exposed population than in other arsenic exposed populations where blackfoot is not reported to occur or seems to occur with less frequency, ie. peripheral vascular lesions reported in vintners in Chile and in a region in Mexico. In 1984, investigators reported that the Blackfoot may be related to a fluorescent arsenic containing compound of unknown structure present in water where Blackfoot is endemic. (ATSDR, 1988). Ergot alkaloids are associated with gangrene in animals (Osweiler, 1985). Ko, 1986 (cited in ATSDR, 1988) reported that the incidence of Blackfoot disease increased (rather than decreased) when arsenic exposure in drinking water was decreased.

The study population was large with more than 40,000 exposed and 7,500 in the control population. The study was not conducted in a blind fashion such that there

may be a basis to find more lesions in the arsenic group and to overlook lesions in the control group (none were reported). However as a study strength 70% of the skin lesions were confirmed by histopathology. There were other chemicals present in the drinking water (including ergot and bacteria), and diet may play a role with a low protein and fat and high carbohydrate (rice) diet. The influence of these uncertainties remains to be determined but they signal a need for cautious characterization of the risk. (EPA, 1988)

Inorganic arsenic is converted in the liver, via methylation, to an organic form that is more readily excreted in the urine by the kidneys. It has been shown that this enzymatic methylation process can be saturated. Blood arsenic levels start to rise when oral intake starts to exceed 200 micrograms/day. If the toxicity of arsenic is due to the inorganic form then higher exposure rates that exceed the bodies ability to methylate and detoxify arsenic then individuals exposed to the higher levels may be at substantially greater risk. Conversely, individuals exposed to low amounts of arsenic may be at substantially less risk than that predicted by extrapolation of effects in the higher exposed populations. This topic is under debate and has not been resolved scientifically at this time.

EPA (1988) listed the following limitations:

1. The potential exposure to sources of arsenic other than drinking water (diet) would result in an overestimation of risk.

2. The higher case-fatality rate and earlier median age for Blackfoot disease may underestimate cancer risk.

3. Differences in diets other than arsenic content between Taiwanese and U.S. populations could modify the carcinogenic response.

The EPA Risk Council (EPA, 1988) stated: "In the Council's view, these qualities and uncertainties could, in a specific risk management situation, modify one's concern downwards as much s an order of magnitude. In such instances, the management documents must clearly articulate this fact and state the factors that influenced such a decision."

REFERENCES

AMERICAN CONFERENCE OF GOVERNMENTAL INDUSTRIAL HYGIENISTS (ACGIH). 1980. Documentation of the Threshold Limit Values. 4th ed. Cincinnati, Ohio. 488 pages.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR). 1987. Draft Toxicological Profile for ARSENIC. Available from: ATSDR Chamblee 28 South, 1600 Clifton Rd. Atlanta, GA, 30333.

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC). 1980. An Evaluation of Chemicals and Industrial Processes Associated with Cancer in Humans Based on Human and Animal Data. IARC Monographs Volumes 1 to 20. Cancer Res. 40:1-12.

NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH (NIOSH). 1982. Registry of Toxic Effects of Chemical Substances. Volumes I-III. U.S. Dept. of Health and Human Services, Cincinnati, OH.

OSWEILER, G. D., T.L. CARSON, W. B. BUCK, AND G. A. VAN GELDER. 1985. Clinical and Diagnostic Veterinary Toxicology. 3rd ed. Dubuque, Iowa: Kendall-Hunt Publ. Co.

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). 1979. Water-Related Environmental Fate of 129 Priority Pollutants. Washington D.C. December 1979. EPA 440/4-79-029.

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). [illegible]a. Ambient Water Quality Criteria for Arsenic. Office of Water Regu[illegible]ns and

Standards, Criteria and Standards Division, Washington D.C. January 1985. EPA 440/5-84-033.

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). 1984b. Health Assessment Document for Inorganic Arsenic. Final Report. Office of Health and Environmental Assessment. Washington, D.C. March 1984. EPA 600/8-83/021F.

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). 1986a. Quality Criteria for Water, 1986 ("The Gold Book"). Office of Water Regulations and Standards, Washington, DC. EPA 440/5-86-001.

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). 1986b. Draft Report: Special Report on Ingested Inorganic Arsenic and Certain Human Health Effects. Prepared by: Office of Pesticides and Toxic Substances, Office of Drinking Water and Office of Research and Development, U.S. Environmental Protection Agency. Prepared for: The Risk Assessment Forum. U.S. Environmental Protection Agency, Washington, D.C. October 30, 1986.

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). 1988. Special Report on Ingested Inorganic Arsenic. Skin Cancer; Nutritional Essentiality. Risk Assessment Forum. Washington, D.C. EPA/625/3-87/013.

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). 1989. Integrated Risk Information System (IRIS). Access Date: June 27, 1989. [Note: This is a computerized data base.]

WEAST, R.E., ed. 1981. Handbook of Chemistry and Physics. 62nd ed. CRC Press, Cleveland, Ohio. 2332 pages.

WORLD HEALTH ORGANIZATION (WHO). 1981. Environmental Health Criteria for Arsenic. 174 pages.

BENZENE

Summary

Benzene is an important industrial solvent and chemical intermediate. It is volatile, and atmospheric photooxidation is probably an important chemical fate process. Data suggest that there is no appreciable bioconcentration or biomagnification of benzene residues.

Benzene is rapidly absorbed through the lungs in humans (approximately 50% for continuous doses of several hours at 50 to 100 ppm); retention is estimated at 30 to 50% of the inhaled dose. Animal studies indicate that absorption is inversely proportional to the exposure concentration. Approximately 90% of orally administered benzene is absorbed. Dermal exposure results in an hourly absorption of 0.4 mg/cm^2. Absorbed benzene is rapidly distributed in the body with high concentrations of the parent compound in bone marrow and adipose tissue and an accumulation of metabolites in bone marrow and liver. It is highly lipid soluble and may accumulate in fatty tissues. Benzene is metabolized primarily in the liver by the mixed function oxidases; the metabolites benzene oxide, catechol, and hydroquinone are believed to be responsible for benzene toxicity. The major route of benzene elimination is urinary excretion of the metabolite phenol. The parent compound is excreted in exhaled air.

The most significant health effects of benzene are hemotoxicity, immunotoxicity and neurotoxicity. Humans exposed to benzene have developed marked hypoplasia of the bone marrow with pancytopenia and aplastic anemia. The immunotoxic effects of benzene include altered serum immunoglobulins and complement levels, antibodies against leukocytes, platelets, and red blood cells, and symptoms of immune stimulation (allergy). Depressed B- and T-cell levels have been produced in animals following inhalation exposure to benzene. Immune dysfunction may play an important role in the carcinogenic potential of benzene. Following an acute or low chronic exposure, symptoms of CNS toxicity have been noted in

humans; disturbed neuronal transport characteristics occur in animals following an acute inhalation exposure.

Benzene has not been shown to produce teratogenic effects even at levels which produce maternal and fetotoxicity in rats. Embryo/fetotoxicity, as measured by a decrease in weight, occurs in rats at levels of 50 to 2,200 ppm benzene; skeletal variants can be found in rats exposed to 125 ppm or higher. Little is known about the reproductive effects of benzene. A study in CD-1 mice suggested a LOAEL of 300 ppm and a NOAEL of 30 ppm for histopathological changes of the ovaries and testes.

A series of epidemiological studies have shown statistically significant associations between leukemia (predominantly myelogenous) and occupational benzene exposure. IARC (1982) has concluded that there is sufficient evidence that benzene is carcinogenic to man. EPA has similarly listed benzene as Group A human carcinogen (USEPA 1989). The Gene-Tox Carcinogenesis Panel categorizes benzene as having sufficient positive evidence for carcinogenicity in animal studies. A study conducted by NTP (1984) (as cited in ATSDR 1987) concluded that there was clear evidence for the carcinogenicity of benzene in both male and female rats and mice after oral administration of the compound. A significant increase in leukemia in mice exposed by inhalation to benzene was reported by Cronkite et al. (1984, 1985) (as cited in ATSDR 1987).

Although benzene has not been shown to be mutagenic in the Salmonella typhimurium assay, in yeast, in the sex-linked recessive lethal mutation assay with Drosophila melanogaster, or in the mouse lymphoma cell forward mutation assay, it has been found to produce chromosomal aberrations in the peripheral lymphocytes and bone marrow cells of humans and animals.

CAS Number: 71-43-2

IUPAC Name: Benzene

Chemical Formula: C_6H_6

Chemical and Physical Properties

Molecular Weight: 78.12

Boiling Point: 80.1°C

Melting Point: 5.56°C

Specific Gravity: 0.88 at 20°C

Solubility in Water: 1,780 mg/liter at 25°C
1,750 mg/liter at 25°C (USEPA 1986a)

Solubility in Organics: Miscible with ethanol, ether, acetic acid, acetone, chloroform, carbon disulfide, and carbon tetrachloride

Log Octanol/Water Partition Coefficient (K_{ow}):

2.01 (Valvani et al. 1980)
2.11 (Geyer et al. 1984)
2.12 (USEPA 1986a)
2.13 (Moriguchi 1975)

Soil/Water Partition Coefficient (K_{oc}):

18-83	Sabljic (1984)
83	Kenaga (1986)

Bioconcentration Factor:

5.2	USEPA (1985) (experimental)
24	USEPA (1980a) (experimental)
24	Davies and Dobbs (1984) Eqn B (log K_{ow} = 2)
19.8	Lyman et al. (1982) Eqn 5-2 (log K_{ow} = 2.01)
23.6	Lyman et al. (1982) Eqn 5-2 (log K_{ow} = 2.11)
24.5	Lyman et al. (1982) Eqn 5-2 (log K_{ow} = 2.13)
18.5	Davies an Dobbs (1984) Eqn C (log K_{ow} = 2.11)
9.3	Davies and Dobbs (1984) Eqn A (S = 1,700)
16.4	Davies and Dobbs (1984) Eqn C (log K_{ow} = 2.13)
28.8	Davies and Dobbs (1984) Eqn B (log K_{ow} = 2.13)

Vapor Pressure: 75 mm Hg at 20°C

	95.2 mm Hg at 25°C (USEPA 1985) 100 mm Hg at 26°C (Perry and Chilton 1973)
Vapor Density:	2.77
Henry's Law Constant:	0.006 atm-m^3/mole (calculated) 5.59 x 10^{-3} atm-m^3/mole (USEPA 1986a)
Flash Point:	-11.1°C

Transport and Fate

Volatization is the major transport process of benzene from surface waters to the ambient air and occurs readily (USEPA 1979). Atmospheric breakdown of benzene is the most likely chemical fate process following its release to air. Although direct oxidation of benzene in environmental waters is unlikely, cloud chamber data indicate that it may be photooxidized rapidly in the atmosphere. The half-life of benzene in air is approximately 6 days (USEPA 1986a). In surface waters, the estimated half-life ranges from 1-6 days (USEPA 1986a).

A range of experimental and estimated soil-water partition coefficients (K_{oc}) is reported above and indicates that some sorption of benzene to soils/sediments and dissolved organic material will occur. Pavlou (1980) estimates that sorption of volatile organic compounds will range from low to moderate. The combined water solubility and low organic partitioning of benzene suggests that this compound will exhibit some degree of environmental mobility.

A range of estimated bioconcentration factors (BCFs) for benzene is also reported above. ATSM (1985) indicates that chemicals with bioconcentration factors (BCFs) less than approximately 100 have low potential for causing harm to wildlife and human health via biomagnification of residues of food chains. The magnitude of

the concentration factors suggests that appreciable bioconcentration or biomagnification of benzene residues is not likely to occur.

Health Effects

1. Pharmacokinetics

Benzene is volatile and lipid soluble; the most frequent route of human exposure is inhalation followed by dermal exposure (USEPA 1980b). Data suggest that after absorption, benzene must be metabolized in order to produce its toxicity (ATSDR 1987).

Studies of benzene absorption following an inhalation exposure indicate that in humans, after continuous doses of 50 to 100 ppm for several hours, approximately 50% of the dose is absorbed. Retention has been reported to be between 30 to 50% of the inhaled dose in humans. In rats and mice, there is an inverse relationship between absorption and inhalation exposure; percent absorbed and retained during a 6-hour exposure of 10 to 1,000 ppm decreased from 33% to 15% in rats and 50% to 10% in mice (ATSDR 1987). After an oral administration, benzene is efficiently absorbed with approximately 90% of the administered dose excreted in exhaled air and urine. Dermal absorption is generally lower than that for inhalation; complete saturation of a human forearm with benzene results in an hourly absorption of 0.4 mg/cm^2 (ATSDR 1987).

After inhalation, approximately 30% of the absorbed dose is distributed to blood, and 50% into bone marrow, adipose tissue and liver. The parent compound concentrates in bone marrow and adipose tissue, whereas metabolites accumulate in bone marrow and liver. Due to its high lipid solubility, benzene may be stored and accumulated in fatty tissues (ATSDR 1987).

The metabolism of benzene takes place primarily in the liver and does not appear to be route specific. Benzene is initially hydroxylated by the mixed function oxidases to the highly reactive intermediate, benzene oxide, which can either spontaneously rearrange to phenol or undergo enzymatic hydration to an epoxide intermediate followed by oxidation to catechol. Hydroquinone is thought to be formed by a second passage of phenol through the mixed function oxidases (USEPA 1980b). Benzene oxide, catechol, and hydroquinone are believed to be the metabolites responsible for benzene toxicity (ATSDR 1987).

Following inhalation exposure in humans, approximately 12 to 50% of the unchanged form is excreted in exhaled air, the metabolites are excreted in urine. Benzene excretion in animals is similar to that in humans. After an oral administration to rabbits, 43% of labelled benzene is exhaled as parent compound and 1.5% as carbon dioxide, suggesting a saturation of the metabolic pathways for benzene. Urinary excretion accounts for 35% of the oral dose; phenol comprises 23% of those metabolites excreted in the urine (ATSDR 1987).

2. Toxicity in Humans and Animals

The target organs for benzene toxicity are primarily bone marrow and the lymphoid system. In addition to its hemotoxic effects, benzene may also induce immunosuppression or sensitization and neurotoxicity.

The oral LD_{50} of benzene has been reported as 0.93 to 5.96 g/kg body weight in male Sprague-Dawley rats and 5.6 g/kg body weight in male Wistar rats. The LC_{50} in female Sprague-Dawley rats is 13,700 ppm following a single 4-hour inhalation exposure (IARC 1982). Lethality from an acute inhalation exposure in humans has been attributed to asphyxiation, respiratory arrest, central nervous system depression or cardiac arrhythmia. A lethal oral dose of benzene in humans has been estimated at 10 ml (8.8g)(ATSDR 1987).

The most significant health effects of benzene are hemotoxicity, immunotoxicity, and neurotoxicity; whereas the metabolites appear to be responsible for the hemotoxicity and immunotoxicity, the parent compound is thought to cause the neurotoxic effects. In humans, hemotoxicity of benzene is characterized after chronic exposure by leucopenia, thrombocytopenia, and anemia. Pancytopenia, an irreversible condition indicating hypoplasia of the bone marrow, has been detected in workers occupationally exposed to high doses of benzene for longer periods of time. The hemotoxic effects have been experimentally reproduced in animals and appear to be independent of route of administration. Leukopenias have been reported in animals after subchronic inhalation exposures of 60 or 88 ppm and after oral doses of 50 mg/kg. In animal studies, however, hemotoxicity does not appear to occur after acute exposures (ATSDR 1987).

Benzene-induced immunotoxicity has been noted in occupationally exposed workers; altered serum immunoglobins and complement levels, antibodies against leukocytes, platelets, and red cells, and symptoms of immune stimulation (allergy) have been reported. Animal studies support the findings of immune dysfunction. Both B- and T-cells have been shown to be significantly depressed by benzene concentrations as low as 10 ppm. Since an important function of the immune system is immuno-surveillance of carcinogenesis, benzene leukemogenesis could be a result of the impairment of this mechanism. No data were found to document the immunotoxicity of benzene after oral or dermal exposure (ATSDR 1987).

Following an acute exposure to benzene in humans, symptoms indicative of CNS toxicity are noted. Acute exposure can result in drowsiness, dizziness, headache, vertigo, delirium or loss of consciousness. Low chronic exposures result in symptoms of CNS lesions. Disturbed neuronal transport characteristics have been noted in animals following acute inhalation of benzene. No data were found demonstrating neurological effects in humans or animals after an oral or dermal exposure (ATSDR 1987).

3. Reproductive and Teratogenic Effects

Benzene crosses the human placenta; however, there is very little known about its effect on developmental toxicity in humans (IARC 1982). Epidemiological studies have been limited by exposure to multiple substances, lack of appropriate controls, problems in identifying exposed populations and a lack of data on exposure levels. A number of studies, however, have evaluated the developmental/maternal toxicity of benzene in animals via the inhalation route. Benzene does not produce teratogenic effects, even at levels that produce maternal toxicity and fetotoxicity. Embryo/fetotoxicity has been demonstrated in rats at levels of 50 to 2200 ppm, with a significant decrease in weight at all dose levels, and skeletal variants found in groups exposed to 125 ppm and higher. There is sufficient evidence to suggest that benzene is not teratogenic or overtly embryotoxic at 10 ppm (ATSDR 1987).

There is little known about the reproductive effects of benzene. A study in CD-1 mice suggested a LOAEL of 300 ppm for histopathological changes in the ovaries (bilateral cysts) and testes (atrophy/degeneration, decrease in spermatozoa, moderate increase in abnormal sperm forms). The NOAEL for these effects was 30 ppm. (ATSDR, 1987).

4. Carcinogenicity

A number of epidemiology studies have associated occupational inhalation exposure to benzene with an increased incidence of leukemia (predominantly myelogenous). Aksoy et al. (1974) (as cited in IARC 1982, USEPA 1980, ATSDR 1987) reported 26 cases of leukemia and a total of 34 leukemias or preleukemias (corresponding to an incidence of 13/100,000 compared to 6/100,000 for the general population) in Turkish workers exposed to benzene; peak exposures were 210 to 650 ppm. A follow-up by Aksoy et al. (1980) (as cited in USEPA 1989) reported an additional 8 cases of leukemia. A retrospective study by Infante (1977), later updated by Rinsky (1981), Rinsky et al. (1987) (as cited in ATSDR 1987, USEPA 1989) of 748 workers, reported a significant increase of myelogenous leukemias at cumulative

exposures less than the equivalent current standard for occupational exposure (10 ppm over a 40 year working lifetime). However, the 8-hour TWA was occasionally exceeded which may have contributed to the excess mortality. Ott (1978) observed 3 leukemia deaths from a cohort of 594 workers exposed to <2 to >25 ppm 8-hour TWA; the increase was not significant. Wong et al. (1983)(as cited in ATSDR 1987) observed dose dependent increases in leukemia, and lymphatic and hematopoietic cancer in a cohort of 4062 workers exposed to <1 to >50 ppm with peaks of >100 ppm. It was noted however that a less than expected incidence of neoplasia in the control population contributed to the finding of a significant increase.

Benzene has been classified by EPA as Group A human carcinogen, in part on the basis of an increased incidence in humans of nonlymphocytic leukemia from occupational exposure and in part on an increased incidence of neoplasia in rats and mice exposed by inhalation or gavage. Cronkite et al. (1984, as cited in ATSDR 1987) exposed C57BL/6 mice to 300 ppm benzene 6 hr/day, 5 days/week, for 16 weeks in order to reproduce the duration and exposure levels of occupational benzene exposure in workers. A significant increase in leukemia was reported. A continuation of the study (Cronkite et al. 1985; as cited in ATSDR 1987) reported a pattern for the lymphoma, with an initial wave beginning at 150 days after exposure, increased mortality at 330 through 390 days and a second wave of lymphoma and solid tumors beginning at 420 days.

NTP (1984) (as cited in ENVIRON Corporation, 1987) concluded that there was clear evidence of carcinogenicity for benzene in F344/N rats and B6C3F1 mice of both sexes. Benzene was administered by gavage in corn oil at doses of 0, 25, 50, 100, or 200 mg/kg to male rats and 0, 25, 50, or 100 mg/kg to female rats and male and female mice. There was a significant increase in neoplasms of the zymbal gland of male and female rats and mice. Male and female rats had increased oral cavity tumors and males had increased skin tumors. Male and female mice exhibited an increased incidence of lymphomas and lung tumors. Male mice were observed to

have harderian and preputial gland tumors and females had mammary gland and ovarian tumors. The increases were generally dose-related.

5. Mutagenicity and Chromosome Aberrations

Benzene has been found to produce chromosome aberrations in peripheral lymphocytes and bone marrow cells from exposed workers (IARC, 1982). Chromosome aberrations have been reported in bone marrow cells from studies in rats, rabbits, mice and amphibians, and in human lymphocyte cultures. Positive results have also been obtained for benzene in the mouse micronucleus assay. Benzene has not been shown to be mutagenic in the Salmonella typhimurium assay, in yeast, in the sex-linked recessive lethal mutation assay with Drosophila melanogaster or in the mouse lymphoma cell forward mutation assay (ATSDR, 1987).

Toxicity to Wildlife and Domestic Animals

The EC_{50} values for benzene in a variety of invertebrate and vertebrate freshwater aquatic species range from 5,300 μg/liter to 386,000 μg/liter (USEPA 1980b). However, only values for the rainbow trout (5,300 μg/liter) were obtained from a flow through test and were based on measured concentrations. Results based on unmeasured concentrations in static tests are likely to underestimate toxicity for relatively volatile compounds like benzene. A chronic toxicity test with Daphnia magna was incomplete, however, no adverse effects were observed at test concentrations as high as 98,000 μg/liter.

For saltwater species, acute values for one fish and five invertebrate species range from 10,900 μg/liter to 924,000 μg/liter (USEPA 1980b). Freshwater and saltwater plant species that have been studies exhibit toxic effects at benzene concentrations ranging from 20,000 μg/liter to 525,000 μg/liter (USEPA 1980b).

Regulations and Standards

The USEPA (1989) report a carcinogenic assessment and drinking water health advisory. Benzene has a classification of A (human carcinogen) based on sufficient evidence of increased incidence of nonlymphocytic leukemia from occupational exposure in humans and an increased incidence of neoplasia in rats and mice exposed by inhalation and gavage. An oral slope factor of 2.9×10^{-2}/mg/kg/day and a drinking water unit risk of 8.3×10^{-7} μg/liter was estimated. Drinking water levels at specified risk levels were identified to be 66 μg/liter (1 in 10,000), 6.6 μg/liter (1 in 100,000), 0.66 μg/liter (1 in 1,000,000) (USEPA 1989). The human respiration rate was assumed to be 20 m^3/day, inhalation absorption was taken as 100% and an air concentration of benzene of 1 ppm was taken to equal 3.25 mg/m^3. The water unit risk was calculated on the assumption that an adult human consumes 2 liters water/day. From the same inhalation exposure data in humans, inhalation risk estimates were also calculated. The inhalation slope factor is reported to be 2.9×10^{-2}/mg/kg/day and the inhalation unit risk to reported to be $8.3 \times 10^{-6}/\mu g/m^3$. Air concentrations at specific risk levels are 10 μg/m^3 (1 in 10,000), 1 μg/m^3 (1 in 100,000), 0.1 μg/m^3 (1 in 1,000,000) (USEPA, 1989).

Ambient Water Quality Criteria (USEPA 1986b):

The available data are not adequate for establishing criteria. However, EPA does report the lowest concentrations of benzene known to cause toxic effects in aquatic organisms.

Aquatic Life (Freshwater)

Acute toxicity:	5,300 μg/liter
Chronic toxicity:	No available data

Aquatic Life (Marine)

Acute toxicity :	5,100 μg/liter
Chronic toxicity:	No available data

National Primary Drinking Water Standard: 0.005 mg/l (40 CFR Part 141)

ACGIH Threshold Limit Value: TWA[1] = 30 mg/m^3
STEL [2] = 75 mg/m^3

OSHA Standards: TWA = 30 mg/m^3
Ceiling Level = 75 mg/m^3
Peak Level = 150 mg/m^3 (10 min.)

D_T Value

The D_T value is defined as that contaminant intake rate (mg/kg/day) that should not induce an adverse effect to human health or should not pose a risk of cancer occurrence greater than a predetermined risk level.

For carcinogens such as benzene, the D_T value is based on the USEPA Cancer Assessment Group's cancer potency slopes. The cancer potency slopes have been estimated for oral exposure routes and for inhalation exposure for some chemicals. The slopes are intended to be a plausible upper bound of the potency of a carcinogen in including cancer at low doses. Calculation of a D_T using a cancer potency slope requires selection of an acceptable cancer risk level. A range of risk levels from 10^{-4} to 10^{-6} is considered for all carcinogens, therefore a range of D_T values is presented. Derivation of the D_T values for benzene is as follows:

$$D_T = \frac{\text{Risk Level}}{\text{Potency Slope / mg/kg/day}}$$

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1 Time Weighted Average.

2 Short Term Effect Level.

$$= \frac{1 \times 10^{-4}}{2.9 \times 10^{-2} \text{ / mg/kg/day}}$$

$$= 3.4 \times 10^{-3} \text{ mg/kg/day}$$

The range of D_T values for benzene is presented below:

Risk	Concentration
10^{-4}	3.4×10^{-3}
10^{-5}	3.4×10^{-4}
10^{-6}	3.4×10^{-5}

References

Agency for Toxic Substances and Disease Registry. U.S. Public Health Service (ATSDR). 1987. Toxicological Profile for Benzene. Draft report.

ASTM. 1985. Standard practice for conducting bioconcentration tests with fishes and saltwater bivalve mollusca. Designation E 1022-84, pages 590-62. In: 1985 Annual Book of ASTM Standards Volume 11.04. American Society for Testing and Materials, Philadelphia, Pennsylvania

American Conference of Governmental Industrial Hygienists (ACGIH). 1980. Documentation of the threshold limit values. 4th ed. Cincinnati, Ohio.

Brief, R.S., J. Lynch, T. Bernath, and R.A. Scala. 1980. Benzene in the workplace. Am. Ind. Hyg. Assoc. J. 41:616-623.

Davies, R.P. and A.J. Dobbs. 1984. The prediction of bioconcentration in fish. Water Res. 18(10):1253-1262.

Dean, B.J. 1978. Genetic toxicology of benzene, toluene, xylenes, and phenols. Mutat. Res. 47:75-97.

ENVIRON Corporation. 1987. Potential health risks from former manufactured-gas plant sites: Toxicity and chemical property profiles. Washington, D.C.

Geyer, H., G. Politzki and D. Freitag. 1984. Prediction of ecotoxicological behavior of chemicals: Relationship between n-octanol/water partition coefficient and bioaccumulation of organic chemicals by Alga Chlorella. Chemosphere. 13(2): 269-284.

Haak, H.L. 1980. Experimental drug-induced aplastic anemia. Clin. Hematol. 9:621-639.

International Agency for Research on Cancer (IARC). 1974. IARC monographs on the evaluation of the carcinogenic risk of chemicals to man. Vol. 7: Some anti-thyroid and related substances, nitrofurans, and industrial chemicals. World Health Organization

International Agency for Research on Cancer (IARC). 1980. An evaluation of chemicals and industrial processes associated with cancer in humans based on human and animal data. IARC Monographs Volumes 1 to 20. Cancer Res. 40:1-12.

International Agency for Research on Cancer (IARC). 1982. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Volume 29: Some industrial chemicals and dyestuffs. World Health Organization, Lyon, France.

Kadeg, R.D., S.I. Pavlou, and A.S. Duxbury. 1986. Elaboration of sediment normalization theory for non-polar hydrophobic organic chemicals. U.S. Environmental Protection Agency, Criteria and Standards Division, Washington, D.C.

Kenaga, E.E. 1980. Correlation of bioconcentration factors of chemicals in aquatic and terrestrial organisms with their physical and chemical properties. Environ. Sci. Technol., 14(5):553-556.

Lyman, W.J. and C.P. Loreti. 1987. Prediction of soil and sediment sorption for organic compounds. Final report. U.S. Environmental Protection Agency,

Monitoring and Data Support Division, Office of Water Regulations and Standards. Washington, D.C.

Lyman, W.J., W.F. Reehl, and D.H. Rosenblatt. 1982. Handbook of chemical property estimation methods: Environmental behavior of organic compounds. McGraw-Hill Book Co., New York.

Moriguchi, I. 1975. Quantitative structure-activity studies: I. Parameters relating to hydrophobicity. Chem. Pharm. Bull. 23(2):247-257.

National Institute for Occupational Safety and Health (NIOSH). 1982. Registry for toxic effects of chemical substances. Volumes I-III. U.S. Department of Health and Human Services. Cincinnati, OH.

Pavlou S.P. 1980. Thermodynamic aspects of equilibrium sorption of persistent organic molecules at the sediment-seawater interface: A framework for predicting distributions in the aquatic environment. In: Contaminants and sediments. Volume 2. Baker, R.A. (editor). Science Publishers, Inc. Ann Arbor, MI.

Perry, R.H. and C.H. Chilton. 1973. Chemical engineers' handbook, 5th edition. McGraw-Hill Book Co., New York, NY.

Rogers, R.D., J.C. McFarlane and A.J. Cross. 1980. Adsorption and desorption of benzene in two soils and montmorillonite clay. Environ Sci. and Technol. 14(4):457-460.

Rosenblatt D.H., T.A. Miller, J.C. Dacre, I. Muul and D.R. Cogley. 1975. Problem definition studies on potential environmental pollutants. II. Physical, chemical, toxicological, and biological properties of 16 substances. Technical

Report 7509. U.S. Army Medical Bioengineering Research and Development Laboratory, Fort Deterick, Frederick, MD.

Sabljic, A. 1984. Predictions of the nature and strength of soil sorption of organic pollutants by molecular topology. J. Agric. Food Chem. 32:243-346.

U.S. Environmental Protection Agency (USEPA). 1979. Water-related environmental Fate of 129 priority pollutants. Washington, D.C. December 1979. EPA 44/4-79-029.

U.S. Environmental Protection Agency (USEPA). 1980a. Identification and listings of hazardous waste under RCRA (Resource Conservation and Recovery Act), Subtitle C, Section 3001; Health and Environmental Effect Profiles (40 CFR 261). USEPA Office of Solid Waste. Washington, D.C. PB81-190019.

U.S. Environmental Protection Agency (USEPA). 1980b. Ambient water quality criteria for DDT. Office of Water Regulations and Standards, Criteria and Standards Division. Washington, D.C. October 1980. EPA 440/5-80-038.

U.S. Environmental Protection Agency (USEPA). 1984. Health effects assessments for DDT. Environmental Criteria and Assessment Office, Cincinnati, Ohio. September 1984. ECAO-CIN-H026 (Final Draft).

U.S. Environmental Protection Agency (USEPA). 1985. Health assessment document for dichloromethane (methylene chloride). Office of Health and Environmental Assessment. Washington, D.C. February 1985. EPA 600/8-82/004F.

U.S. Environmental Protection Agency (USEPA). 1986a. Superfund public health evaluation manual. Office Emergency and Remedial Response. Washington, D.C. EPA 540/1-86/060.

U.S. Environmental Protection Agency (USEPA). 1986b. Quality criteria for water, 1986 ("The Gold Book"). Office of Water Regulations and Standards, Washington, D.C. EPA 440/5-86-001.

U.S. Environmental Protection Agency (USEPA). 1989a. Integrated Risk Information System (IRIS). Access Date: June 27, 1989. [Note: This is a computerized data base.]

Valvani, S.C., S.H. Yalkowsky and T.J. Roseman. 1980. Solubility and partitioning. IV. Aqueous solubility and octanol-water partition coefficients of liquid nonelectrolytes. J. Pharm. Sci. 70(5):502-505.

Waldron, H.A. 1979. Target Organs: The Blood. J. Soc. Occup. Med. 29:65-71.

CARBON TETRACHLORIDE

Summary

Carbon tetrachloride is a colorless, water insoluble, volatile liquid that is miscible with most organic solvents. In the past, it was widely used as a solvent and dry cleaning agent, but its use for these purposes was banned by the U.S. Food and Drug Administration in 1970. Today it is used primarily in the synthesis of chlorofluoromethanes (compounds which are used as refrigerants, foam-blowing agents solvents, in degreasing products, and fire extinguishers) and as a grain fumigant and pesticide. In 1980, 70 million pounds of carbon tetrachloride were manufactured in the U.S. (USITC 1981). Air, water and foodstuffs are all potential exposure sources for the general population, as carbon tetrachloride is very stable in the environment with an atmospheric life-time of 60-100 years. It is acutely toxic; death has occurred in humans following ingestion of 1.5-3.0 ml or inhalation of 280 ppm. The main health effects of carbon tetrachloride are due to its actions on the liver, kidneys and brain. These effects are markedly enhanced by the concurrent consumption of alcohol or other substances that increase the microsomal enzyme drug metabolism system, such as barbiturates. Carbon tetrachloride is an animal carcinogen, causing liver tumors in mice, rats and hamsters, and a probable human carcinogen.

CAS Number:	56-23-5
Chemical Formula:	CCl_4
IUPAC Name:	Tetrachloromethane
Synonyms:	perchloromethane, carbon tet, carbon chloride, carbona

Chemical and Physical Properties

Molecular Weight:	153.82
Boiling Point:	76.5°C (Merck 1983)

	76.7°C (Verschueren, 1983)
Melting Point:	-22.9°C
Specific Gravity:	1.59 at 20°C (liquid) (Perry and Chilton 1973) 5.3 vapor (gas) 5.5 (Verschueren, 1983)
Solubility in Water:	800 mg/liter (Rogers et al. 1980) 780 mg/liter (Davies and Dobbs 1984) 930 mg/liter (Valvani et al. 1980)
Solubility in Organics:	Miscible with alcohol, benzene, chloroform, ether and carbon disulfide
Log Octanol/Water Partition Coefficient (K_{ow}):	2.64 (Neely et al. 1974) 2.73 (Davies and Dobbs 1984; Rogers 1980) 2.78 (Geyer et al. 1984) 2.83 (Valvani et al. 1980)

Soil/water Partition Coefficient (K_{oc}):

72	Sabljic (1984)
45	Rogers et al. (1980) Table V (experimental)
102-112	Lyman et al. (1982) Eqn 4-5 (S=780-930)
328; 462	Lyman and Loreti (1987) (log Kow=2.64; 2.83)
650; 825	Lyman et al. (1982) (Eqn 4-8; Kow=2.64; 2.83)

Bioconcentration Factor:

17	Neely et al. 1974 (experimental)
72	Davies and Dobbs (1984) Eqn B (log Kow=2.8)
69.95	Lyman et al. (1982) Eqn 5-2 (log Kow=2.73)
76.3	Lyman et al. (1982) Eqn 5-2 (log Kow=2.78)
83.3	Lyman et al. (1982) Eqn 5-2 (log Kow=2.83)
13.7; 77	Davies and Dobbs (1984) Eqn 3 (S=855; 40)
30	Davies and Dobbs (1984) Table 2 (experimental)
36	Davies and Dobbs (1984) Eqn C (log Kow=2.8)
79	Lyman et al. (1982) Eqn 5-2 (log Kow=2.8)
30	Barrows et al. (1980) (experimental)

Vapor Pressure: 90 mm Hg at 20°C (USEPA, 1986)
100 mm Hg at 23°C (Perry and Chilton 1973)
115.2 mm Hg at 25°C (Johns 1976)

Vapor Density: 5.32

Henry's Law Constant: 2.4 x 10-2 atm-m3/mole
1.01 dimensionless (USEPA, 1986)

Odor Threshold: 21.4 ppm in air (Fazzalari, 1978)
50 mg/l in water (Verschueren, 1983)

Transport and Fate in the Environment

Carbon tetrachloride has a high vapor pressure and therefore volatilizes rapidly into the atmosphere from surface water and from surface soils. A range of experimental and estimated soil-water partition coefficients (K_{oc}) is reported above and indicates that sorption of carbon tetrachloride to soils and sediments and dissolved organic material will occur. Pavlou (1980) estimates that sorption of volatile organic compounds will range from low to moderate. The combined water solubility and organic partitioning of carbon tetrachloride suggests that this compound will exhibit some degree of environmental mobility.

Carbon tetrachloride is very stable in the atmosphere as it does not react with hydroxyl radicals that initiate the breakdown and transformation of other volatile hydrocarbons (ATSDR 1988). Additionally, carbon tetrachloride is not subject to photolysis in the troposphere (Davis et al. 1975). The atmospheric lifetime has been estimated to range from 60-100 years (USEPA 1984). In order for photodegradation to occur, the compound must diffuse to the stratosphere where the more prevalent, shorter ultraviolet light will attack the molecule to yield free chlorine atoms and trichloromethane radicals (Molina and Rowland 1974).

Carbon tetrachloride in water also does not photodegrade or oxidize and has an estimated half-life of 7000 years at a concentration of 1 ppm, a pH of 7.0 and a temperature of 25°C (Mabey and Mill 1978). The physical and chemical properties of this compound favor volatilization from water to air.

A range of experimental and estimated bioconcentration factors (BCFs) for carbon tetrachloride is also reported above. ASTM (1985) indicates that chemicals with bioconcentration factors less than approximately 100 have low potential for causing harm to wildlife and human health via biomagnification. The magnitude of the concentration factors suggest that appreciable bioconcentration or biomagnification of carbon tetrachloride residues is not likely to occur.

Background Exposure

Since carbon tetrachloride is readily volatilized, most of the compound will exist in air. There are no known natural sources of carbon tetrachloride and its presence in the environment is attributable to direct release to the atmosphere during production or use of the agent. A significant amount is also generated from photodegradation of perchloroethylene, another widely used industrial solvent (Letkiewicz et al. 1983).

Concentrations of carbon tetrachloride in air were monitored from various locations across the U.S. and found to range from nondetectable to 70 $\mu g/m^3$ (11 ppb; Brodzinski and Singh 1983). Average values were 0.8 $\mu g/m^3$ in rural areas, 1.2 $\mu g/m^3$ in suburban and urban areas, and 3.7 $\mu g/m^3$ near emission sources (Brodzinski and Singh 1983). With these values, an estimated typical carbon tetrachloride exposure level of 0.1 $\mu g/kg/day$ has been reported (ATSDR 1988). Carbon tetrachloride is also a common contaminant in indoor air with concentrations in some homes as high as 1 $\mu g/m^3$, due to the presence of carbon tetrachloride-containing building materials and household products (Wallace 1986).

Carbon tetrachloride is a contaminant in water supplies in the U.S., although 99% of all groundwater supplies and 95% of all surface water supplies contain less than 0.5 ug/liter (ATSDR 1988). By comparison, typical values for carbon tetrachloride in chemical waste sites range from 50 to 1000 ug/liter (ATSDR 1988). From the data available, a typical exposure level in water has been estimated at 0.01 ug/kg/day (ATSDR 1988). There is no information available on background exposure levels for carbon tetrachloride in soil or foodstuffs.

Health Effects

Human Data

The major pathological effects following exposure to carbon tetrachloride by either ingestion or inhalation are liver and kidney damage, with death often attributable to acute hepatic and/or renal failure. There are many reports of accidental poisoning and deaths in humans due to inhalation of carbon tetrachloride fumes, with the lethal exposure level dependent on the amount of compound present and the duration of the exposure. There are reports of deaths after ingestion of as little as 1.5-3.0 ml of carbon tetrachloride or inhalation of as little as 280 ppm (USEPA 1984).

Isolated reports of liver cancer in humans have been made following both acute (Tracey and Sherlock 1968) and long-term (Johnstone 1968) exposure to carbon tetrachloride fumes. However, adequate epidemiological studies have not been performed to support the conclusion that carbon tetrachloride is a human carcinogen. Therefore, it is considered a suspected human carcinogen, based on the strength of the animal data.

The principal clinical signs of carbon tetrachloride exposure are a swollen and tender liver, elevated serum levels of hepatic enzymes (such as alanine amino transferase, ALT), elevated serum bilirubin levels, and decreased serum levels of

liver proteins (such as albumin)(USEPA 1984). In cases of death after acute exposures, histological findings on autopsy include hepatitis, hepatic fat accumulation, and pronounced centrilobular necrosis (Umiker and Pearce 1953; Jennings 1955). The levels of carbon tetrachloride exposure which can produce these hepatotoxic effects in humans are not well-defined, although levels for a lowest-observed-adverse-effect-level (LOAEL) and a no-observed-adverse-effect-level (NOAEL) have been reported. A NOAEL of approximately 10 ppm was reported by Stewart et al. (1961) after 70-180 minute exposures to carbon tetrachloride produced no changes in serum hepatic enzyme levels. The same study established 50 ppm as a LOAEL because a slight decrease in serum iron levels was seen at this dose.

In addition to hepatotoxic actions, carbon tetrachloride is a potent nephrotoxic agent in humans. Nephritis and nephrosis are common following inhalation or oral exposures (Norwood et al. 1950; Jennings 1955). The clinical signs of renal dysfunction which develop within hours to days of carbon tetrachloride exposure are anuria, albuminuria, edema, and hypertension (ATSDR 1988). Following fatal carbon tetrachloride exposures, autopsy and histological examination usually reveal mild degeneration of the kidney (Norwood et al. 1950; Jennings 1955). The exposure levels which lead to renal damage in humans are not well-defined, although there are reports of proteinuria in workers exposed acutely to as little as 200 ppm carbon tetrachloride (Barnes and Jones 1967). A NOAEL of approximately 10 ppm for 180 minutes exposure to carbon tetrachloride has been reported for renal effects (Stewart et al. 1967).

Other immediate symptoms of carbon tetrachloride exposure (lethal or life-threatening levels) include severe abdominal pain, nausea and vomiting, and depending on the dose, gastric and intestinal hemorrhages. Exposures to concentrations around 100 ppm (nonlethal) result in less severe but similar symptoms (Kazantis and Bromford 1960 as cited in USEPA 1984). Concurrent central nervous system symptoms are dizziness, headache, confusion, semiconsciousness, and delirium

(Torkelson and Rowe 1981). Effects on other organ systems, such as the eyes, respiratory and cardiovascular systems, have been reported, although these effects appear to be secondary to severe renal injury and/or central nervous system depression rather than direct actions of carbon tetrachloride on lung or cardiac tissue (ATSDR 1988). In one recent report, chronic lymphocytic leukemia has been linked to occupational exposure to a number of solvents, including carbon tetrachloride (Linet and Blattner 1985).

All of the above effects of carbon tetrachloride are markedly enhanced by the concurrent consumption of alcohol or other substances that increase the microsomal enzyme drug metabolism system, such as barbiturates. In addition, people suffering from pulmonary diseases, gastric ulcers, liver or kidney diseases, diabetes, or glandular disturbances may be especially sensitive to the effects of carbon tetrachloride.

Animal Data

As in humans, the hepatotoxic effects of carbon tetrachloride exposure are the most prominent of its systemic actions. Unlike humans, renal injury does not often occur in animals following inhalation of carbon tetrachloride; however, the kidney is a target organ after oral administration of the compound (ATSDR 1988). In rats, exposure to 10 to 50 ppm carbon tetrachloride (acute or subchronic) results in mild to moderate liver injury with signs such as elevated serum hepatic enzyme levels and inflammation (Adams et al. 1952; David et al. 1981; Paustenbach et al. 1986). Long-term exposure to lower levels (1 to 5 ppm) of carbon tetrachloride did not produce any significant changes in liver function in rats, monkeys or guinea pigs (Adams et al. 1952; Prendergast et al. 1967).

The oral LD_{50} for carbon tetrachloride is 2920 mg/kg in the rat, 12800 mg/kg in the mouse, 6380 mg/kg in the rabbit, and 3680 mg/kg in the hamster (Torkelson and Rowe 1981). Carbon tetrachloride is a mild eye and weak skin irritant, and is not a skin sensitizer.

There are many animal studies which have examined the effects of oral carbon tetrachloride exposure on hepatic function, but only a few have examined its dose-dependent effects. Single oral doses of 40 and 80 mg/kg produced changes in hepatic histology and increased liver weight in rats (Eschenbrenner and Miller 1946; Bruckner et al. 1986). Longer-term oral exposures of 20 mg/kg/day for 11 weeks produced mild signs of liver injury while 80 mg/kg/day produced severe hepatic injury (Bruckner et al. 1986). Doses lower than 20 mg/kg/day were also tested for 12 weeks and it was found that 1 mg/kg/day of carbon tetrachloride produced no hepatic effects, 10 mg/kg/day resulted in mild centrilobular vacuolization, and 33 mg/kg/day produced extensive hepatic damage (Bruckner et al. 1986). There is only one report of chronic exposure to carbon tetrachloride (oral) where no significant effects were seen on serum liver enzymes or hepatic fat content in rats given 10 to 18 mg/kg/day for 2 years (Alumot et al. 1976).

As discussed previously, oral administration of carbon tetrachloride in animals produces nephrotoxicity, although the kidney is less sensitive to the effects of this agent than the liver (ATSDR 1988). A progressive increase in the size of the kidney and changes in the histology of kidney tissue have been seen after acute exposure to 4000 mg/kg of carbon tetrachloride in rats (Striker et al. 1968). Marginal indications of kidney injury were seen in mice exposed to 2500 mg/kg/day for 14 days or 1200 mg/kg/day for 90 days, doses which produce severe hepatic injury (Hayes et al. 1986).

Reproductive Toxicity

There is no information available on the reproductive effects of carbon tetrachloride in humans; however, several studies have been performed in animals. Decreases in fetal body weight and crown-rump length have been observed in offspring of rats exposed 7 hrs/day to either 300 or 1000 ppm carbon tetrachloride on days 6 through 15 of gestation (Schwetz et al. 1974 as cited in USEPA 1984). Upon gross examination of the fetuses, subcutaneous edema was seen in animals exposed to 300 ppm, and an increased incidence of sternebral anomalies was seen in those animals exposed to 1000 ppm carbon tetrachloride. While hepatotoxicity was evident in the dams, as indicated by increased SGPT activity, there was no evidence of hepatotoxicity in the pups. In another study, there was a slightly decreased viability in rat pups following exposure of dams for 8 hrs/day on days 10-15 of gestation to 250 ppm carbon tetrachloride (Gilman 1971 as cited in USEPA 1984). Small areas of focal hepatic damage have been reported among rat pups of dams injected with 1600 mg/kg of carbon tetrachloride subcutaneously on days 19 or 20 of gestation, and among nursing neonates whose dams were injected once with 1600-3200 mg/kg of this agent (Bhattacharyya 1965 as cited in USEPA 1984).

Degenerative changes in testicular histology which eventually resulted in aspermatogenesis and functional infertility has been reported following intraperitoneal injection of male rats with a relatively high dose of carbon tetrachloride, 4800 mg/kg (Chatterjee 1966 as cited in USEPA 1984).

Mutagenicity

Carbon tetrachloride has been tested for mutagenic potential in bacterial, yeast, and mammalian cell test assays and found to be negative in almost all cases (USEPA 1984). It has been noted, however, that none of the negative studies adequately demonstrated that biotransformation of carbon tetrachloride to its reactive intermediates had occurred in the systems studied (USEPA 1984). One in vivo study attempted to address this problem by using Saccharomyces cerevisiae strain D7 which

contains an endogenous cytochrome P450 monooxygenase system capable of activating carbon tetrachloride (Callen et al. 1980). The results showed that exposure to carbon tetrachloride increased gene conversion, mitotic crossing over, and gene reversion. The combined mutagenicity data indicate that carbon tetrachloride is at best a weak mutagen.

Carcinogenicity

Carbon tetrachloride is an animal carcinogen. It produces hepatocellular carcinomas in all animal species evaluated (rats, mice and hamsters) and is often used as a positive control in the investigation of carcinogenic potential of other chemical compounds. Increases in the incidence of hepatomas have been observed in mice receiving 30 doses of 160 mg/kg over 90 days (Eschenbrenner and Miller 1946), and in virtually all mice treated with 1250 and 2500 mg/kg carbon tetrachloride by gavage 5 times each week for 78 weeks (NCI 1976). All hamsters that received 30 weekly doses of 10-20 mg carbon tetrachloride and survived for 10 or more weeks after cessation of the treatment were found to have liver cell carcinomas (Della Porta et al. 1961). Hepatocarcinomas have also been reported in rats following 7 months of chronic inhalation exposure (dose and schedule unspecified) (Costa et al. 1963 as cited in IARC 1979), and following subcutaneous injections of 2000 mg/kg 2 times/week for 68 weeks (Reuber and Glover 1970 as cited in IARC 1979). An increased incidence of mammary adenocarcinomas was observed in female rats following subcutaneous injections of 160 mg/kg of carbon tetrachloride 2 times/week for 2 years (Alpert et al. 1972 as cited in IARC 1979).

Pharmacokinetics and Metabolism

Carbon tetrachloride is absorbed rapidly after ingestion or inhalation, but more slowly through the skin. About 30% of an inhaled dose is absorbed (McCollister et al. 1952) and between 60-80% of an oral dose is absorbed (Reddrop et al. 1981; Paul

and Rubenstein 1963). In a radioactive tracer study in monkeys, carbon tetrachloride was shown to be readily distributed to all major organs, with highest concentrations found in adipose tissue, liver, bone marrow, blood, brain, and kidneys (McCollister et al. 1952). Approximately 50% of an inhaled dose of carbon tetrachloride is exhaled unchanged. Elimination of an oral dose has an estimated half-life of 4-6 hours, with most of the dose eliminated within 2 days (USEPA 1985).

The metabolism of carbon tetrachloride in humans has not been investigated; however, there is a large amount of data in laboratory animals. Metabolism in animals occurs mainly in the liver, and the severe hepatotoxicity and other toxic effects seen with this compound are dependent upon its biotransformation and activation by the liver mixed function oxidase system (USEPA 1984). The first step is thought to be formation of a trichloromethyl radical which can then undergo several anaerobic reactions to form either chloroform, hexachloroethane, or carbon monoxide. Aerobic metabolism of the trichloromethyl radical results in formation of the highly reactive carbonyl chloride (phosgene) and carbon dioxide (ATSDR 1988). The carbon dioxide and chloroform which are formed during carbon tetrachloride metabolism are excreted in the expired air of experimental animals (USEPA 1985). The highly reactive phosgene and other free radicals (i.e. trichloromethane) which are formed during metabolism are thought to initiate the lipid peroxidation process which is the most important factor in carbon tetrachloride-induced liver damage. Lipid peroxidation in rats has been shown to be preferentially induced at low oxygen partial pressures (DeGroot et al. 1988) and can be prevented or reduced by pretreatment of rats with Vitamin E, which raises the liver antioxidant level and prevents the liver necrosis caused by carbon tetrachloride exposure (Danni et al. 1988). Carbon tetrachloride-induced lipid peroxidation may also be inhibited by trapping or scavenging the metabolite lipid radicals by such compounds as 5,10-dihydroindeno[1,2-b]indole (Shertzer 1988). Free radicals may also be responsible for damage in the lung, kidneys, testes, adrenals, and placenta which is observed following carbon tetrachloride exposure (USEPA 1984).

Immune System

Two recent unconfirmed reports in the Russian literature suggest carbon tetrachloride may affect organs of the immune system in rats in a direct and indirect manner (Kolpashcikova 1988a and 1988b). Another report (Kaminski et al. 1989) showed that repeated i.p. injection of carbon tetrachloride to B6C3F1 mice resulted in marked depression of both humoral and cell-mediated immune response at concentrations that also affected the liver.

Toxicity to Wildlife and Domestic Animals

Carbon tetrachloride has been shown to be acutely toxic to a number of aquatic species at concentrations as low as 35 mg/liter. However, the majority of these studies were performed under static conditions and due to its volatility may have underestimated the acute toxicity of carbon tetrachloride (USEPA 1980). In a static chamber study with bluegill sunfish (Lepomis macrochirus) a 96-hour LC_{50} value of 125 ppm (125 mg/liter) was reported (Dawson et al. 1977). A 48-hour EC_{50} of 35.2 mg/liter was reported for cladoceran (Daphia magna) (USEPA 1978). Another freshwater study in two species of carp (Cyprinus carpio and Carassius auratus) examined the toxic effects of carbon tetrachloride on liver and kidney tissue. Histological changes were observed in liver tissue of both species at doses of 0.3-5.0 ml/kg for 8 days (Jiang and Zhang 1979).

A number of marine species have also been tested for sensitivity to carbon tetrachloride toxicity. A 24-hour median tolerance limit of 320 mg/liter was reported in brine shrimp (Price and Conway 1974). Acute LD_{50} values were also reported for marine pinperch (Lagodon rhomeboides) and marine flatfish (Limanda limanda) at 175 mg/liter and 115 mg/liter respectively (Garrett 1957; Pearson and McConnell 1975). In an acute study with the sheepshead minnow (Cyprinodon variegatus) the observed-no-effect concentration was reported to be 130 mg/liter (Heitmuller et al. 1981).

The reproductive toxicity of carbon tetrachloride was examined in a number of freshwater fish and amphibian species following exposure to the compound at fertilization through development up to 4 days post-hatching. LC50 values ranged from 1.16 to 22.42 mg/liter of carbon tetrachloride, with the greatest susceptibility shown in rainbow trout, the Leopard frog (Rana pipiens), and the European Common frog (Rana temporaria)(Black et al. 1982). The median lethal concentration of carbon tetrachloride at 4 days posthatching was 1.97 mg/liter in rainbow trout and 1.64 mg/liter in the Leopard frog. It was estimated that concentrations of 30 ug of carbon tetrachloride/liter of water would adversely affect sensitive aquatic species (Black et al. 1982).

There are a few reports of low lethal dose (LD_{LO}) values for carbon tetrachloride in domestic animals. The values reported were for dogs, 1000 mg/kg (NIOSH 1982) and for cats, 38110 ppm/2 hrs (NIOSH 1982). An intravenous LD_{50} value has also been reported for rabbits at 5840 mg/kg (NIOSH 1982).

Regulations and Standards

The USEPA (1988) report an oral Reference Dose (RfD) for noncarcinogenic effects of carbon tetrac' oride as well as a carcinogenic assessment and drinking water health advisories. The RfD was derived based on a subchronic rat gavage study which identified dose-response effects of carbon tetrachloride on liver lesions (Bruckner et al. 1986). A NOAEL of 1 mg/kg/day and a LOAEL of 10 mg/kg/day were reported, and from these values an RfD was estimated to be 7×10^{-4} mg/kg/day.

1 mg/kg/day (NOAEL) x 5/7 = 0.71 mg/kg/day (5 day/week dosing regimen)

$$\frac{0.71 \text{ mg/kg/day}}{1000} = 7 \times 10^{-4} \text{ mg/kg/day} = \text{RfD (UF=1000)}$$

An uncertainty factor (UF) of 1000 is applied to the NOAEL to account for interspecies and intraspecies variability, as well as extrapolation from subchronic to chronic exposure. The USEPA (1989) expresses "medium" confidence in this RfD and they state that, "The principal study was well-conducted and good dose-response was observed in the liver, which is the target organ for {carbon tetrachloride} toxicity; thus, high confidence was assigned. Four additional subchronic studies support the RfD, but reproductive and teratology endpoints are not well investigated; thus, the data base rates a medium confidence."

Carbon tetrachloride has a classification of B2 (probable human carcinogen) based on sufficient carcinogenicity data in rats, mice and hamsters. In all three species, oral administration of carbon tetrachloride produced hepatocellular carcinomas (USEPA 1988). With the supporting data, an oral slope factor of 1.3×10^{-1} and an oral unit risk of 3.7×10^{-6} μg/liter in drinking water was estimated. Drinking water levels at specified risk levels were identified to be 30 ug/liter (1 in 10,000), 3 μg/liter (1 in 100,000), and 0.3 μg/liter (1 in 1,000,000). From the same oral exposure data in animals, inhalation risk estimates were also calculated. The inhalation slope factor is reported to be 1.3×10^{-1} and the unit cancer risk is reported to be 1.5×10^{-5} $\mu g/m^3$. Air concentrations at specific risk levels are 7 $\mu g/m^3$ (1 in 10,000), 0.7 $\mu g/m^3$ (1 in 100,000), and 0.07 $\mu g/m^3$ (1 in 1,000,000) (USEPA 1988). The inhalation unit risk was calculated assuming 20 m^3/day of air intake and 40% of the carbon tetrachloride dose absorbed in humans.

Because of the carcinogenic potential and well-characterized adverse health effects of carbon tetrachloride, there are a number of regulations and guidelines which are listed in Table I.

TABLE I

Agency	Description	Value
WHO	Guidance for Drinking Water, Tentative	0.003 mg/l
OSHA	Permissible Exposure Limit	
	Time-Weighted Average	10 ppm
	Ceiling	10 ppm
	Maximum Peak	200 ppm
USEPA Office of Drinking Water	Maximum Contaminant Level	0.005 mg/l
ACGIH	Threshold Limit Value	5 ppm
NIOSH	Recommended Exposure Limit for Occupational Exposure Ceiling	2 ppm
	Immediately Dangerous to Life or Health Level	300 ppm
USEPA Office of Drinking Water	Health Advisories	
	1 day	4 mg/l
	10 day	1.6×10^{-1} mg/l
	longer term	
	adult	2.5×10^{-1} mg/l
	child	7.1×10^{-2} mg/l
USEPA	Ambient Water Quality Criteria water and organisms	
	10^{-4}	40 µg/l
	10^{-5}	4.0 µg/l
	10^{-6}	0.4 µg/l

D_T Value

The D_T value is defined as that contaminant intake rate (mg/kg/day) that should not induce an adverse effect to human health or should not pose a risk of cancer occurrence greater than a predetermined risk level.

For carcinogens such as carbon tetrachloride, the D_T value is based on the USEPA Cancer Assessment Group's cancer potency slopes. The cancer potency slopes for oral exposure and for inhalation exposure are based on oral dosing studies in rats, mice, and hamsters where carbon tetrachloride produced hepatocellular carcinomas. The slopes are intended to be a plausible upper bound of the potency of a carcinogen in inducing cancer at low doses. Calculation of a D_T using a cancer potency slope requires selection of an acceptable cancer risk level. A range of risk levels from 10^{-4} to 10^{-6} is considered for all carcinogens, therefore a range of D_T values is presented. Derivation of the D_T values for carbon tetrachloride is as follows:

$$D_T = \frac{\text{Risk Level}}{\text{Potency Slope (mg/kg/day)}^{-1}}$$

$$= \frac{1 \times 10^{-4}}{1.3 \times 10^{-1} \text{ (mg/kg/day)}^{-1}}$$

$$= 7.7 \times 10^{-4} \text{ (mg/kg/day)}$$

The range of D_T values for carbon tetrachloride is presented below:

Risk Level	D_T Oral Exposure (mg/kg/day)	D_T Inhalation Exposure (mg/kg/day)
	10^{-4}	7.7×10^{-4} 7.7×10^{-4}
	10^{-5}	7.7×10^{-5} 7.7×10^{-5}
	10^{-6}	7.7×10^{-6} 7.7×10^{-6}

A corresponding second set of potency factor values (presented below, as taken from USEPA 1984) were derived from the MLE estimate from the multistage model, and the geometric mean of the 4 data sets was also derived. Also presented is the time-to-tumor data which was available (only 2 data sets) and the estimates based on the use of the time-to-tumor model.

	Multistage*		Time-to-Tumor*	
Data Set	MLE	UL	MLE	UL
Della Porta et al. (1961)	7.4E-1	1.2	-	-
Edwards et al. (1942)	2.5E-1	3.3E-1	-	-
NCI (1976) mouse	4.9E-2	6.3E-2	6.3E-2	7.7E-2
NCI (1976) rat	6.7E-3	1.1E-2	1.1E-2	1.9E-2
All (geometric mean)	8.8E-2	1.3E-1**	2.6E-2	3.9E-2

* All values are expressed as (mg/kg/day)-1; MLE = Maximum Likelihood Estimate; UL = upper 95% confidence limit

** This value is the CAG potency slope value.

The multistage model based DT values would be:

Risk Level	Geometric Mean of MLE based	Geometric Mean of UL based (CAG values)
10-4	1.1 x 10-3	7.7 x 10-4
10-5	1.1 x 10-4	7.7 x 10-5
10-6	1.1 x 10-5	7.7 x 10-6

The time-to-tumor model based D_T values would be:

Risk Level	Geometric Mean of MLE based	Geometric Mean of UL based
10-4	3.8 x 10-3	2.6 x 10-3
10-5	3.8 x 10-4	2.6 x 10-4
10-6	3.8 x 10-5	2.6 x 10-5

The D_T values calculated from the geometric mean of the MLE (multistage model) differ from the CAG potency based D_T's by a factor of 1.4, with the CAG based values being more conservative. The difference in these two data sets is only that the CAG data uses the geometric mean UL value from the multistage model (data shown in table 2 above) which accounts for estimation errors due to small sample size (USEPA 1984). The D_T values calculated from the geometric mean of the MLE (time-to-tumor model) differ from the CAG D_T's by a factor of 4.9, with the time-to-tumor data being less conservative. The UL based D_T values of the time-to-tumor model are also less conservative than the CAG D_T's by a factor of 3.4.

References

Adams, E.M., H.C. Spencer, V.K. Rowe et al. 1952. Vapor toxicity of carbon tetrachloride determined by experiments on laboratory animals. Arch. Ind. Hyg. Occup. Med. 6:50-66.

Agency for Toxic Substances and Disease Registry (ATSDR). 1988. Carbon tetrachloride, draft report. TP-ATSDR-0608-CTC.

Alumot, E., E. Nachtomi, E. Mandel, P. Holstein, A. Bondi, and M. Herzberg. 1976. Tolerance and acceptable daily intake of chlorinated fumigants in the rat diet. Food Cosmet. Toxicol. 14:105-110.

Barnes, R. and R.C. Jones. 1967. Carbon tetrachloride poisoning. Am. Ind. Hyg. Assoc. J. 28:557-560.

Barrows, M.E., S.R. Petrocelli, K.J. Macek, and J.J. Carrol. 1980. Bioconcentration and elimination of selected water pollutants by bluegill sunfish (Lepomis macrochirus). In: Dynamics, Exposure, and Hazard Assessment of Toxic Chemicals, R. Haque, ed. Ann Arbor Science Publ., Inc. Ann Arbor, MI.

Black, J.A., W.J. Birge, W.E. McDonnell, A.G. Westerman, and B.A. Ramey. 1982. The aquatic toxicity of organic compounds to embryo-larval stages of fish and amphibians. Kentucky Water Resources Research Institute, Lexington, KY. Sponsored by Office of Water Research and Technology, Washington, D.C. PB82-224601.

Brodzinski, R. and H.B. Singh. 1983. Volatile organic chemicals in the atmosphere: An assessment of available data. Research Triangle Park, NC: USEPA, Office of Research and Development. EPA-600/3-83-027(A).

Bruckner, J.V., W.F. MacKenzie, S. Muralidhara, R. Luthra, G.M. Kyle, and D. Acosta. 1986. Fund. Appl. Toxicol. 6:16-34.

Callen, D.F., C.R. Wolf and R.M. Philpot. 1980. Cytochrome P-450 mediated genetic activity and cytotoxicity of seven halogenated aliphatic hydrocarbons in Saccharomyces cerevisiae. Mutat. Res. 77:55-63.

Cox, R.A., R.G. Derwent and A.E.J. Eggleton. 1976. Photochemical oxidation of halocarbons in the troposphere. Atmos. Environ. 10:305-308.

Danni, O., M. Aragno and G. Ugazio. 1988. In vivo studies on halogen compound interactions. I. Effects of carbon tetrachloride plus 1,2-dibromoethane on liver necrosis. Res. Commun. Chem. Pathol. Pharmacol. Sep. 61(3): 377-390.

David, A., E. Frantik, R. Holusa et al. 1981. Role of time and concentration on carbon tetrachloride toxicity in rats. Int. Arch. Occup. Environ. Health. 48:49-60.

Davies, R.P. and A.J. Dobbs. 1984. The prediction of bioconcentration in fish. Water Res. 18(10): 1253-1262.

Davis, D.D., J.F. Schmidt, C.M. Neeley et al. 1975. Effect of wavelength in the gas-phase photolysis of carbon tetrachloride at 253.7, 184.9, 147 and 106.7 nm. J. Phys. Chem. 79:11-7.

Dawson, G.W., A.L. Jennings, D. Drozdowski, and E. Rider. 1977. The acute toxicity of 47 industrial chemicals to fresh and saltwater fishes. J. Hazard. Mat. 1:303-318.

DeGroot, H., A. Littauer, D. Hugo-Wissemann et al. 1988. Lipid peroxidation and cell viability in isolated hepatocytes in a redesigned oxystat system: evaluation of the hypothesis that lipid peroxidation, preferentially induced at low oxygen partial pressures, is decisive for CC14 liver cell injury. Arch. Biochem Biophys. 264: 591-599.

Della Porta, G., B. Terracini and P. Shubik. 1961. Induction with carbon tetrachloride of liver cell carcinomas in hamsters. J. Natl. Can. Inst. 26:855-863.

Eschenbrenner, A.B. and E. Miller. 1946. Liver necrosis and the induction of carbon tetrachloride hepatomas in strain A mice. J. Natl. Cancer Inst. 6:325-341.

Fazzalari, F.A. (ed.). 1978 Compilation of odor and taste threshold values data. ASTM Data Series DS 48A (Committee E-18). Philadelphia, PA: American Society for Testing and Materials, P. 33.

Garrett, J.T. 1954. Toxicity investigations on aquatic and marine life. Public Works. 88:95-96.

Geyer, H., G. Politzki, and D. Freitag. 1984. Prediction of ecotoxicological behavior of chemicals: Relationship between n-octanol-water partition coefficient and bioaccumulation of organic chemicals by Alga Chlorella. Chemosphere, 13(2): 269-284.

Hayes, J.r., L.W. Condie, and J.F. Berzelleca. 1986. Acute, 14-day repeated dosing, and 90-day subchronic toxicity studies of carbon tetrachloride in CD-1 mice. Fund. Appl. Toxicol. 7:454-463.

Heitmuller, P.T., T.A. Hollister, and P.R. Parrish. 1981. Acute toxicity of 54 industrial chemicals to sheephead minnows (Cypinodon variegatus). Bull. Environ. Contam. Toxicol. 27:596-604.

International Agency for Research on Cancer (IARC). 1979. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Some Halogenated Hydrocarbons. Volume 20.

Jennings, R.B. 1955. Fatal fulminant acute carbon tetrachloride poisoning. Arch. Pathol. 59:269-284.

Jiang, L. and R. Zhang. 1979. Histological studies on the toxic effects of phenol and CCl_4 on the liver and kidney of common carp and Crucian carp. Acta. Zool. Sin. 25:311-314.

Johns, R. 1976. Air pollution assessment of carbon tetrachloride. Prepared by Mitre Corporation for U.S. Environmental Protection Agency. Mitre Corp., Washington, DC. Contract No. 68-02-1495.

Johnstone, R.T. 1948. Occupational medicine and industrial hygiene. St. Louis, MO: CV Mosby Co., pp. 148-158.

Kaminski, N.E., S.D. Jordan and M.P. Holsapple. 1989. Suppression of humoral and cell-mediated immune responses by carbon tetrachloride. Fund. Appl. Toxicol. 12:117-128.

Kopashchikova, I.F. 1988a. Changes in the immune system under long-term intoxication by carbon tetrachloride. Gig. Sanit. 12:81-83.

Kopashchikova, I.F. 1988b. Effect of long-term intoxication with carbon tetrachloride on changes in the immune system. Gig. Sanit. 12: 81-83.

Letkiewicz, F., P. Johnston, C. Macaluso et al. 1983. Carbon tetrachloride: occurrence in drinking water, food, and air. Washington, DC. USEPA, Office of Drinking Water.

Linet, M.S. and W.A. Blattner. 1988. The epidemiology of chronic lymphocytic leukemia. Chronic lymphocytic leukemia. Polliack, A. and D. Catovsky eds. New York: Harwood Academic Publishers. pp. 11-32.

Lyman, W.J. and C.P. Loreti. 1987. Prediction of soil and sediment sorption for organic compounds. Final Report. U.S. Environmental Protection Agency, Monitoring and Data Support Division, Office of Water Regulations and Standards. Washington DC.

Lyman, W.J., W.F. Reehl, and D.H. Rosenblatt. 1982. Handbook of chemical property estimation methods: Environmental behavior of organic compounds. McGraw-Hill Book Co., New York.

Mabey, W. and T. Mill. 1978. Critical review of hydrolysis or organic compounds in water under environmental conditions. J. Phys. Chem. Ref. Data. 7:383-415.

McCollister, D.D., W.H. Reamer, G.J. Atchison, and H.C. Spencer. 1952. The absorption, distribution, and elimination of radioactive carbon tetrachloride by

monkeys upon exposure to low vapor concentrations. J. Pharmacol. Exp. Ther. 102:112-124.

Molina, M.J. and F.S. Rowland. 1974. Predicted present stratospheric abundances of chlorine species from photodissociation of carbon tetrachloride. Geophys. Res. Lett. 1:309-312.

National Cancer Institute (NCI). 1976. Report on carcinogenesis bioassay of carbon tetrachloride. Bethesda, MD. National Cancer Institute, March 1, 1976.

National Institute for Occupational Safety and Health (NIOSH). 1982. Registry of toxic effects of chemical substances. Volumes I-III. Department of Health and Human Services. Cincinnati, OH.

Neeley, W.B. et al. 1974. Partition coefficient to measure bioconcentration potential of organic chemicals in fish. Environ. Sci. Technol. 8:1113.

Norwood, W.D., P.A. Fuqua, and B.C. Scudder. 1950. Carbon tetrachloride poisoning Arch. Ind. Hyg. Occup. Med. 1:90-100.

Paul, B.P. and D. Rubinstein. 1963. Metabolism of carbon tetrachloride and chloroform by the rat. J. Pharmacol. Exp. Ther. 141:141-148.

Pavlou, S.P. 1980. Thermodynamic aspects of equilibrium sorption of persistent organic molecules at the sediment-Seawater interface: A framework for predicting distributions in the aquatic environment. In: Contaminants and Sediments. Volume 2. Baker, R.A. (Editor). Science Publishers, Inc., Ann Arbor, MI.

Paustenbach, D.J., Christian, J.E. and G.P. Carlson. 1986. The effect of an 11.5-hr/day exposure schedule on the distribution and toxicity of inhaled carbon tetrachloride in the rat. Fund. Appl. Toxicol. 6:472-483.

Pearson, C.R. and G. McConnell. 1975. Chlorinated C_1 and C_2 hydrocarbons in the environment. Proc. R. Soc. London B. 189:305-332.

Perry, R.H. and C.H. Chilton. 1973. Chemical Engineer's Handbook, 5th edition. McGraw-Hill Book Co., New York, NY.

Prendergast, J.A., R.A. Jones, L.J. Jenkins and J. Siegel. 1967. Effects on experimental animals of long-term inhalation of trichloroethylene, carbon tetrachloride, 1,1,1-trichloromethane, dichlorofluoromethane, and 1,1-dichloroethylene. Toxicol. Appl. Pharmacol. 10:270-289.

Price, K., G. Waggy and R. Conway. 1974. Brine shrimp bioassay and seawater BOD (biochemical oxygen demand) of petrochemicals. J. Water Pollut. Control Fed. 46:63-77.

Reddrop, C.J., W. Riess, and T.F. Slater. 1981. Interactions of carbon tetrachloride and promethazine in the rat. II. Elimination of carbon tetrachloride and chloroform in expired air as indications of their metabolism in the intact animal. Biochem. Pharmacol. 30:1449-1445.

Rogers, R.D., J.C. McFarlane, and A.J. Cross. 1980. Adsorption and desorption of benzene in two soils and montmorillonite clay. Environ. Sci. Technol. 14(4)457-460.

Sabljic, A. 1984. Predictions of the nature and strength of soil sorption of organic pollutants by molecular topology. J. Agric. Food Chem. 32:243-246.

Shertzer, H.G. and M. Sainsbury. 1988. Protection against carbon tetrachloride hepatotoxicity by 5, 10-dihydroindeno [1,2-b] indole, a potent inhibitor of lipid peroxidation. Food Chem. Toxicol. 26: 517-522.

Stewart, R.D., H.H. Gay, D.S. Erley et al. 1961. Human exposure to carbon tetrachloride vapor. J. Occup. Expos. 3:586-590.

Striker, G.E., E.A. Smuckler, P.W. Kohnen et al. 1968. Structural and functional changes in rat kidney during CCl_4 intoxication. Am. J. Pathol. 53:769-789.

Tracey, J.P. and P. Sherlock. 1968. Hepatoma following carbon tetrachloride poisoning. New York J. Med. 68:2202-2204.

Torkelson, T.K. and V.K. Rowe. 1981. Halogenated aliphatic hydrocarbons. In: Patty's Industrial Hygiene and Toxicology. 3rd edition. G.D. Clayton and F.E. Clayton, eds. Vol 2B. John Wiley and Sons, New York.

Umiker, W. and J. Pearce. 1953. Nature and genesis of pulmonary alterations in carbon tetrachloride poisoning. Arch. Pathol. 55:203-217.

United States Environmental Protection Agency (USEPA). 1978. In-depth studies of health and environmental impacts of selected water pollutants. Contract No. 68-01-4646, USEPA, Cincinnati, OH.

United States Environmental Protection Agency (USEPA). 1980. Ambient Water Quality Criteria for Carbon Tetrachloride. EPA 440/5-80-026.

United States Environmental Protection Agency (USEPA). 1984. Health Assessment Document for Carbon Tetrachloride, Final Report. USEPA-600/8-82-001F.

United States Environmental Protection Agency (USEPA). 1985. Carbon Tetrachloride, Health Advisory, Office of Drinking Water.

United States Environmental Protection Agency (USEPA). 1988. Integrated Risk Information Service, Washington, DC, updated 6/30/88.

United States International Commission (USITC). 1981. Preliminary report on U.S. production of selected synthetic organic materials.

Valvani, S.C., S.H. Yalkowski, and T.J. Roseman. 1980. Solubility and partitioning. IV. Aqueous solubility and octanol-water partition coefficients of liquid nonelectrolytes. J. Pharm. Sci. 70(5):502-505.

Verschueren, K. 1983. Handbook of environmental data of organic chemicals. 2nd ed. New York, NY: Van Nostrand Reinhold Co., p. 341.

Wallace, L.A. 1986. Personal exposures, indoor and outdoor air concentrations and exhaled breath concentrations of selected volatile organic compounds measured for 600 residents of New Jersey, North Dakota, North Carolina and California. Toxicol. Environ. Chem. 12:215-236.

CHLORDANE

Summary

Chlordane is an organochlorine pesticide that was registered for use in the United States from 1948 to 1988. It was used on field crops until 1978 and until 1988 could be applied to soil for control of structural pests (termites) in homes. Technical chlordane is a complex mixture that includes two isomers of chlordane, heptachlor, and two isomers of nonachlor. It is very persistent in the environment and is readily bioaccumulated in fish and other aquatic organisms. Chlordane causes liver tumors in mice, however, generally mutagenicity assays were negative which is consistent with an epigenetic mechanism of carcinogenicity (ATSDR, 1988). Chlordane has produced some positive results in a few assays including sister chromatid exchange in human lymphoid cells. It causes adverse reproductive effects in mice, and chronic exposure causes liver changes and adversely affects the central nervous system. Chlordane is very toxic to aquatic organisms.

Chlordane has been detected in rural and urban air in average concentrations ranging from not detected to 58 ng/m^3 with most values less than 1 ng/m^3. Levels in indoor air were higher with average values up to 1900 ng/m^3 with most average values in the 1 to 500 ng/m^3 range. (Table 5-1, ATSDR, 1988).

Chlordane has been detected in surface waters at levels in the range of 0.1 ppb with higher levels (1 to 100 ppb) in sediments. Soil levels reported for urban and rural soils are in the range of 0.002 ppm (Everglades National Park) to 4 ppm (Hartford, CT.) Rural soil levels are on the order of 0.02 to 0.2 ppm. (Table 5-3, ATSDR, 1988). Generally less than 1% of composited food samples had detectable levels of chlordan with the few positives reported in the 1 to 30 ppb range. (Table 5-4, ATSDR, 1988)

Chlordane residues have also been reported in a variety of fish samples (levels

generally in the 20 to 100 ppb range) (Table 5-5, ATSDR 1988) and in a variety of terrestrial organisms including birds and mammals. (Table 5-6, ATSDR, 1988).

Chlordane has also been detected in human blood samples at levels from not detected to 550 ppb. For example, human daily intake in 1981 was estimated to be 2 to 4 ng/kg per day from food for a 16 to 19-year-old male. (Table 5-8, ATSDR, 1988)

Technical chlordane is a complex mixture; however, the major components are cis-chlordane and trans-chlordane. The technical product also contains a variety of other chlorinated hydrocarbons, including heptachlor. It is a viscous amber-colored liquid. Much of the available literature does not distinguish between the chlordane isomers and appears to discuss mixtures of these compounds.

CAS Number: Chlordane (mixture): 57-74-9
cis-Chlordane: 5103-74-2
trans-Chlordane: 5103-71-9
Chemical Formula: $C_{10}H_6Cl_8$
IUPAC Name: 1,2,4,5,6,7,8,8-Octachloro-2,3,3a,4,7,7a-hexahydro-4, 7-methanoindene
Important Synonyms and Trade Names: cis-chlordane: alpha-chlordane
trans-chlordane: gamma-chlordane

Chemical and Physical Properties

Molecular Weight: 409.3
Boiling Point: 175C at 2 mm Hg
Melting Point: cis-chlordane: 107-109C, trans-chlordane: 103-105C
Specific Gravity: 1.59-1.635 at 16C (technical chlordane)
Solubility in Water: From 0.056 to 1.85 mg/liter at 25C
Solubility in Organics: Miscible in aliphatic and aromatic solvents (technical chlordane)

Log Octanol/Water Partition Coefficient (K_{ow}):

2.78; 3.32; 5.48 Kadeg, et al (1986) literature values

Soil-Water Partition Coefficient (K_{oc}):

422; 53,570	Lyman and Loreti (1987) (log K_{ow} = 2.78; 5.48;
21,300	Kenaga (1980)
624; 53,850	Kadeg, et al (1986) (log K_{ow} = 2.78; 5.48)
141,200	Kadeg, et al (1986) (literature value)
140,000	USEPA (1986)
775; 22,810	Lyman, et al (1982) Eqn 4-8 (log K_{ow} = 2.78; 5.48)

Bioconcentration Factor: DATA MISSING

Vapor Pressure: 1 x 10^{-5} mm Hg at 20°C (USEPA 1986)

Flash Point: Minimum 81°C (technical chlordane)

Henry's Law Constant: 9.6 x 10^{-5} atm-m^3/mole (calculated)

9.63 x 10^{-6} atm-m^3/mole (USEPA 1986)

4.05 x 10^{-4} Dimensionless

Transport and Fate

Chlordane is very persistent in the environment, resisting chemical and biological degradation into less harmful substances. Chlordane is virtually insoluble in water. Chlordane present in clear water may be somewhat volatile, and this may be an important loss process. Less loss of chlordane from aquatic systems will occur when organics are present due to adsorption processes. Therefore, residue concentrations in sediment are often much higher than in water.

Chlordane binds tightly to soil particles and persists for years in soils after surface

application. A range of experimental and estimated soil-water partition coefficients (K_{oc}) is reported above and indicates that sorption of chlordane to soils/sediments and dissolved organic material will occur. Pavlou (1980) estimates that sorption of organochlorine pesticides is very high; therefore, little environmental mobility would be expected for this compound.

Chlordane applied as an emulsifiable concentrate is more readily volatilized than when applied as a granular formulation. Certain food and feed crops can accumulate residues by absorption from the soil. Chlordane has been found to accumulate in the peels of root vegetables studied (Rosenblatt, et al 1975). The persistence (half-life) of Chlordane in soil ranges from 2 to greater than 13 years (Rosenblatt, et al 1975). Atmospheric transport of vapors and contaminated dust particles from soil application sites can occur. Chlordane exhibits strong tendencies for bioaccumulation in some aquatic and terrestrial organisms. It can concentrate at levels thousands of times greater than the surrounding water medium in a variety of aquatic organisms, including bacteria, algae, daphnids, and fish (USEPA 1980). ASTM (1985) indicates that chemicals with bioconcentration factors less than approximately 100 have low potential for causing harm to wildlife and human health via biomagnification of residues up food chains. The magnitude of the concentration factors suggests that bioconcentration or biomagnification of chlordane residues will occur.

Health Effects

Several strains of mice fed diets containing analytical-grade chlordane for 80 weeks exhibited a highly significant dose-dependant incidence of liver tumors (males and females). For rats NCI reported neoplastic nodules but not carcinomas and the response was in the low but not the high dose group. In the NCI study the response was in female rats but not in male rats. Some older rat studies also reported liver enlargement and lesions but not tumors. In a more recent study a non-statistically significant (ATSDR, 1988; reported as a significant increase in USEPA, 1989)

increase in liver adenomas occurred in male, but not female, F344 rats in the high dose group. At the time this was prepared there appears to be some debate about the presence and nature of the liver lesions in the male rats. The July 1989 IRIS chlordane file reports that after a review of the pathology it was concluded that liver lesions (tumors?, other?) had not occurred in male rats but that hypertrophy (not tumors) had occurred in the female rats. Later in the same IRIS file it is reported in the carcinogenicity section that malignant liver tumors were induced in F344 male rats, but later the narrative only discusses adenomas (non-malignant tumors) in the liver. ATSDR, 1988 reports that there was no statistically significant increase in tumor incidence in the Velsicol F344 rats study. (EPA has been contacted but the issue has not been resolved at the time this document was prepared)

Chlordane has been classified in EPA's Group B2, according to EPA's Proposed Guidelines for Carcinogen Risk Assessment, based upon the positive results of these studies (50 Federal Register 46988, Wed. Nov. 13, 1985). Chlordane has induced mutagenic effects in at least one test system. Negative results were obtained in chromosome aberration tests utilizing Chinese hamster ovary cells (NTP 1985); however, positive evidence of sister chromatid exchange was obtained in the same test medium.

Reproductive effects, including developmental defects and neonatal metabolic and biochemical disorders, are observed in the offspring of mice exposed to chlordane. Tests with laboratory animals, primarily rodents, have demonstrated acute and chronic toxic effects. Mixtures of the two isomers appear to exhibit similar toxicities to that of single isomers. Chronic exposure to chlordane causes liver changes and induces or suppresses a variety of enzyme systems. In addition, chlordane may act as a cumulative neurotoxin. Acute effects include anorexia, weight loss, tremors, convulsions, and death. The oral LD50 in the rat is 283 mg/kg. Oxychlordane, an epoxide metabolite formed from either chlordane isomer, is more acutely toxic than chlordane. The oral LD50 of oxychlordane administered to rats in corn oil is 19

mg/kg, and 43 mg/kg when administered in an aqueous suspension.

Clinical symptoms of acute oral or dermal exposure to chlordane in humans include vomiting, seizures, electroencephalographic dysrhythmia, convulsions, and possible death. Oxychlordane has been found in a high percentage of sampled human adipose tissues and also in milk samples.

Toxicity to Wildlife and Domestic Animals

Chlordane or oxychlordane residues have been found in a wide variety of wildlife and domestic animal species, but usually at relatively low levels. Studies indicate that chlordane may produce toxic effects in certain soil invertebrates after surface application. Although little information concerning bioaccumulation in these organisms is available, the potential bioaccumulation of chlordane or oxychlordane by terrestrial insectivores is of concern. Little information on the toxic effects of chlordane to mammalian wildlife and domestic animal species is available. Chlordane or oxychlordane residues have been found in crops, meat, fish and poultry, dairy products, and eggs. Generally less than 1% of composited food samples had detectable levels of chlordane with the few positives reported in the 1 to 30 ppb range. (Table 5-4, ATSDR, 1988)

Oral LD5O values for chlordane ranging from 331 to 858 ppm in the diet (approximately 25-50 mg/kg) are reported for a variety of wild bird species. Oral LD5O values ranging from 100 to 1,000 mg/kg are reported for a variety of animals, including rodents, goats, sheep, and chickens.

Regulations and Standards

WHO	Guidelines for drinking water	0.3 ug/l	ATSDR, 1988
FA/WHO	Acceptable Daily Intake	0-0.001 mg/kg	ATSDR, 1988
OSHA	PEL-8 hour	0.5 mg/m3	ATSDR, 1988
NRC	Interim Guideline for Military Housing	5 ug/M3	ATSDR, 1988
RfD	EPA	5 X 10-5 mg/kg	ATSDR, 1988

State	Drinking Water Concentrations range from several states	0.22-3 ug/l	ATSDR, 1988

Ambient Water Quality Criteria (USEPA 1986):

Aquatic Life (Freshwater)

Acute toxicity: 2.4 ug/liter

Chronic toxicity: 0.0043 ug/liter

Aquatic Life (Saltwater)

Acute toxicity: 0.09 ug/liter

Chronic toxicity: 0.0040 ug/liter

Human Health

Due to the carcinogenicity of chlordane, the ambient water criterion is set at zero. However, estimates of the carcinogenic risks due to ingestion of contaminated water and contaminated aquatic organisms are:

Risk	Concentration
10^{-4}	46 ng/liter
10^{-5}	4,6 ng/liter
10^{-6}	0.46 ng/liter

National Primary Drinking Hater Standard: 0.005 mg/liter (Proposed MCL; 50 Federal Register 46904, Wednesday November 13, 1985)

CAG Potency Slope for Oral Exposure (USEPA 1989): 1.3 (mg/kg/day)-1

CAG Potency Slope for Inhalation (USEPA 1989): 1.3 (mg/kg/day)-1

OSHA Standard (skin): TWA[1] = 0.5 mg/M^3

ACGIH Threshold Limit Values (skin): TWA = 0.5 mg/m^3

STEL[2] = 2 mg/m^3

Department of Transportation: Combustible liquid

RANGE OF D_t VALUES

The D_t value is defined as that contaminant intake rate (mg/kg/day) that should not induce an adverse effect to human health or should not pose a risk of cancer occurrence greater than a predetermined risk level.

There are a number of plausible D_t values that might be protective of human health. The first D_t value is based on the USEPA Carcinogen Assessment Group's cancer potency slopes using the mouse liver tumor data. The slopes are intended to be a

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1 Time Weighted Average

2 Short Term Effect Level

plausible upper bound of the potency of a carcinogen in inducing cancer at low doses. Calculation of a D_t using a cancer potency slope requires selection of an acceptable cancer risk level. A range 10-4 to 10-7 is considered for all carcinogens, therefore a range of D_t values is presented. Derivation of the D_t values for chlordane is as follows:

$$D_t = \frac{\text{Risk Level}}{\text{Potency Slope (mg/kg/day)-1}}$$

$$= \frac{1 \times 10^{-4}}{1.3 \text{ (mg/kg/day)-1}}$$

$$= 7.7 \times 10^{-5} \text{ mg/kg/day}$$

The range of D_t values based on carcinogenic potency for chlordane (oral and inhalation) is presented below:

Risk Level	D_T (mg/kg/day)
10^{-4}	7.7×10^{-5}
10^{-5}	7.7×10^{-6}
10^{-6}	7.7×10^{-7}

The second D_t is based on the EPA RfD which is 6×10^{-5} mg/kg or about 25 % less than the cancer based D_t at the 10-4 risk level. Since chlordane may be acting through some non-genotoxic mechanism (ATSDR, 1988) the second D_t is based on non-cancer end points. The RfD is based on 1/1000 th of the no effect level for liver lesions in a 30 month (lifetime) feeding study in rats. Note that the RfD is based on effects in the same target organ as the cancer based D_t. The 1000 fold safety factor, rather than the more typical 100 fold, was used since there are not fully adequate

reproduction studies. From a toxicology standpoint, it is unlikely that reproductive effects would occur at a dose below that causing minor liver lesions in a lifetime study that would not in turn be protected against by a 100 fold safety factor off of a no-effect level in a 30 month study.

The second D_t = 6×10^{-5} mg/kg.

The third D_t is based on the conventional EPA approach for deriving an RfD for protection against threshold effects recognizing the probable non-genotoxic action of chlordane. It is derived from the no-effect level for liver lesions in a 30 month rat feeding study, and incorporates an uncertainty factor of 100.

The third D_t is = 6×10^{-4} mg/kg, which is 6 times greater than the 10^{-4} cancer risk based dose.

The fourth D_t is based on the upper value for the WHO ADI which is 1×10^{-3} mg/kg.

The fourth D_t is = 1×10^{-3} mg/kg, 13 times the 10^{-4} cancer risk based dose.

CERTAINTIES AND UNCERTAINTIES OF DIFFERENT DT VALUES AND UNDERLYING TOXICOLOGY

At the 10^{-4} risk level the 4 D_ts developed above differ by only 1 order of magnitude. However, as the risk level decreases (10^{-5}, 10^{-6}) the differences become larger, 2 or 3 orders of magnitude.

The key uncertainty with the chlorinated hydrocarbons that readily produce liver tumors in mice is the relevance of the mouse liver to humans. This is presently an area of controversy and the available science does not provide an absolute answer. There does not appear to be readily available epidemiology data to assist in resolving the issue. The NRC in 1982 set an air standard for military housing of 5 ug/M^3

which in the adult would deliver a 1.5×10^{-3} mg/kg dose-rate based on 24 hours of exposure. This is close to the WHO ADI value. At least the first 3 D_t values (7.7×10^{-5} at 10^{-4} risk level, 5×10^{-5} and 5×10^{-4}) are all based on liver effects. It is plausible that if chlordane is acting through some non-genotoxic mechanism then acceptable dose levels based on no-effect levels in the liver (target organ) could be protective even if chlordane is a human carcinogen.

REFERENCES

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY. 1988. Draft Toxicological Profile for Chlordane. U.S. Public Health Service.

AMERICAN CONFERENCE OF GOVERNMENTAL INDUSTRIAL HYGIENISTS (ACGIH). 1980. Documentation of the Threshold Limit Values. 4th ed. Cincinnati, Ohio. 488 pages.

ASTM. 1985. Standard Practice for Conducting Bioconcentration Tests with Fishes and Saltwater Bivalve Mollusca. Designation E 1022-84, pages 590-62. In: 1985 Annual Book of ASTM Standards Volume 11.04. American Society for Testing and Materials, Philadelphia, Pennsylvania.

ATTALLAH Y.H., D.M. WHITACRE, and B.L. HOO. 1979. Comparative Volatility of Liquid and Granular Formulations of Chlordane and Heptachlor from Soil. Bull. Environ. Contam. Toxicol. 22:570-574.

DAVIES, R.P. and A.J. DOBBS. 1984. The Prediction of Bioconcentration in Fish. Water Res. 18(10):1253-1262.

ECAO 1980 (see USEPA 1980).

KADEG, R.D. , S.P. PAVLOU, and A.S. DUXBURY. 1986. Elaboration of Sediment Normalization Theory for Non Polar Hydrophobic Organic Chemicals. U.S. Environmental Protection Agency, Criteria and Standards Division, Washington D.C.

KENAGA, E.E. 1980. Correlation of Bioconcentration Factors of Chemicals in Aquatic and Terrestrial Organisms with Their Physical and Chemical Properties.

Environ. Sci. Technol., 14(5): 553-556.

LYMAN, W.J., and C.P. LORETI. 1987. Prediction of Soil and Sediment Sorption for Organic Compounds. Final Report. U.S. Environmental Protection Agency, Monitoring and Data Support Division, Office of Water Regulations and Standards. Washington D.C.

LYMAN, W.J., W.F. REEHL, and D.H. ROSENBLATT. 1982. Handbook of Chemical Property Estimation Methods: Environmental Behavior of Organic Compounds. McGraw-Hill Book Co. , New York.

NATIONAL CANCER INSTITUTE (NCI). 1977. Bioassay of Chlordane for Possible Carcinogenicity. National Cancer Institute Carcinogenesis Technical Report Series No. 8. Bethesda, Maryland. DHEW Publication NO. (NIH) 77-808.

NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH (NIOSH). 1982. Registry of Toxic Effects of Chemical Substances. Volumes I-III. Dept. of Health and Human Services. Cincinnati, OH.

NATIONAL RESEARCH COUNCIL OF CANADA. 1974. Chlordane: Its Effects on Canadian Ecosystems and its Chemistry. Subcommittee on Pesticides and Related Compounds. Subcommittee Report No. 2. Ottawa, Canada. Publication No. NRC 14094 of the Environmental Secretariat.

NATIONAL TOXICOLOGY PROGRAM (NTP) . 1985. Fiscal Year 1985 Annual Plan. U.S. Department of Health and Human Services. Public Health Service. Washington, D.C. NTP-85-055.

PAVLOU, S.P. 1980. Thermodynamic Aspects of Equilibrium Sorption of Persistent Organic Molecules at the Sediment-Seawater Interface: A Framework For

Predicting Distributions in the Aquatic Environment. IN: Contaminants and Sediments. Volume 2. Baker, R.A. (Editor). Science Publishers, Inc. Ann Arbor, MI.

ROSENBLATT D.H., T.A. MILLER, J.C. DACRE, I. MUUL and D.R, COGLEY. 1975. Problem Definition Studies on Potential Environmental Pollutants. II. Physical, Chemical, Toxicological, and Biological Properties of 16 Substances. Technical Report 7509. U.S. Army Medical Bioengineering Research and Development Laboratory, Fort Detrick, Frederick, MD.

THE MERCK INDEX. 1976. Ninth ed. Windhoiz, M., ed. Merck and Co., Rahway, New Jersey.

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). 1976. Draft Environmental Impact Statement Concerning Notice of Intent to Cancel Registered Uses of Products Containing Chlordane and Heptachlor. Washington, D.C. August 1976. EPA 540/4-76-003.

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). 1976. Pesticidal Aspects of Chlordane and Heptachlor in Relation to Man and the Environment--A Further Review, 1972-1975. Washington, D.C. August 1976. EPA 540/4-76-005.

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). 1979. Water-Related Environmental Fate of 129 Priority Pollutants. Washington D.C, December 1979. EPA 440/4-79-029.

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). 1980. Ambient Water Quality Criteria for Chlordane. Office of Water Regulations and Standards, Criteria and Standards Division, Washington D.C. October 1980. EPA

440/5-80-027.

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). 1984. Health Effects Assessment for Chlordane. Environmental Criteria and Assessment Office, Cincinnati, Ohio. September 1984. ECAO-CIN-H023 (Final Draft). U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). 1986. Superfund Public Health Evaluation Manual. Office of Emergency and Remedial Response. Washington D.C. EPA 540/1-86/060.

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). 1989. Integrated Risk Information System (IRIS). Access Date: June 27, 1989. [Note: This is a computerized data base.]

WORTHING, C.R., ed. 1979. The Pesticide Manual--A World Compendium. British Crop Protection Council, Croydon, England. 655 pages.

CHLOROFORM

Summary

Chloroform (trichloromethane) is often produced during the chlorination of drinking water and thus is a common drinking water contaminant. Chloroform has been detected in 99.5% of U.S. finished drinking water samples. (ATSDR, 1989) Typical concentrations are in the range of 32-68 ug/L and typical water intakes are calculated to be 64 to 132 ug/person/day. (ATSDR, 1989)

Typical U.S. air levels are in the range of 0.02 to 13 ug/M^3. Indoor air samples are in the range of 0.07 to 3.6 ug/M3. (ATSDR, 1989) Daily exposure due to inhalation is calculated to be 4 to 260 ug/person/day. Chloroform levels in food are in the range of 1 to 180 ppb but the data are not sufficient to estimate a daily average intake.

Chloroform at one time was used as an inhalation anesthetic humans at air concentrations of 8000-10000 ppm with blood concentrations of 80 to 165 mg/l. (ATSDR, 1989) Occupational exposures to levels of 22 to 71 ppm were not associated with liver damage.

It is volatile in surface waters and is not likely to be persistent in the environment. Chloroform causes an increase in kidney epithelial tumors in rats and in hepatocellular carcinomas in mice. " The overwhelmingly negative nature of the results from multiple laboratories in a spectrum of in-vitro, in vivo, prokaryotic and eukaryotic test systems strongly suggests that chloroform is either not genotoxic or very weakly positive (Shell, 1988) or .." may be mutagenic, but no definitive conclusion can be reached concerning mutagenicity of chloroform" ATSDR, 1989. "There are no epidemiologic studies on chloroform itself. ... Several ecological and case-control studies of populations consuming chlorinated drinking water in which chloroform was

the major chlorinated organic show small significant increases in the risk of rectal, bladder or colon cancer on an intermittent basis. Many other suspected carcinogens were also present in these water supplies." (USEPA, 1989). "Although it can be concluded that the human data suggest a possible increased risk of cancer at these three sites because chloroform is the predominant trihalomethane in drinking water, the data are too weak to draw a conclusion about the carcinogenic potential of chloroform." (ATSDR, 1989 citing EPA 1985). Other toxic effects of chloroform include central nervous system depression; eye, skin, and gastrointestinal irritation; and damage to the liver, heart, and kidney.

CAS Number: 67-66-3
Chemical Formula: $CHCl_3$
IUPAC Name: Trichloromethane

Chemical and Physical Properties

Molecular Weight: 119.38
Boiling Point: 61.7 C
Melting Point: -63.5 C
Specific Gravity: 1.4832 at 20 C
Solubility in Water: 8,200 mg/liter at 20 C
7,500 mg/liter at 20 C (Valvani, 1980)
9,200 mg/liter at 25 C (Davies and Dobbs 1984)

Solubility in Organics: Soluble in acetone, miscible with alcohol, ether, and benzene

Log Octanol/Water Partition Coefficient (K_{ow}): 1.97 Moriguchi (1975)
1.90 (Davies and-Dobbs 1984)
1.96 (Valvani et al. 1980)

Soil-Water Partition Coefficient (K_{oc}):

45	Sabljic (1984)
257;281	Lyman et al., (1982) Eqn 4-8 (log K_{ow} =1.9; 1.97)
87; 99	Lyman and Loreti (1987) (log K_{ow} 1.90; 1.97)

Bioconcentration Factor (BCF):

16	Lyman et al., (1982) Eqn 5-2 (log K_{ow} = 1.9)
18.18	Lyman et al., (1982) Eqn 5-2 (log K_{ow} = 1.96)
3.59; 4.03	Davies and Dobbs (1984) Eqn A (S. 7,500, 9,200)
21	Davies and Dobbs (1984) Eqn B (log K_{ow} = 1.9)
12	Davies and Dobbs (1984) Eqn C (log K_{ow} = 1.9)

Vapor Pressure: 150.5 mm Hg at 20 C

200 mm Hg at 25.9 C (Perry and Chilton, 1973)

Vapor Density: 4.12

Henry's Law Constant: 3.9 x 10^{-3} atm-m^3/mole (calculated)

2.87 x 10^{-3} atm-m^3/mole (USEPA 1985a)

1.21 x 10^{-1} Dimensionless

Transport and Fate

Due to its high vapor pressure, volatilization is the major transport process for removal of chloroform from aquatic systems (USEPA 1979). Once in the troposphere, chloroform is attacked by hydroxyl radicals with the subsequent formation of phosgene (COCl2) and possibly chlorine oxide (ClO) radicals. Neither of these reaction products is likely to persist; phosgene is readily hydrolyzed to hydrochloric acid and carbon dioxide. Reaction with hydroxy radicals is thought to be the primary environmental fate of chloroform. However, chloroform that remains in the troposphere may return to Earth in precipitation or adsorbed on particulates,

and a small amount may diffuse upward to the stratosphere where it photodissociates via interaction with light (USEPA 1985b). Neither photolysis or hydrolysis, appear to be significant environmental fate processes for chloroform (USEPA 1985b).

A range of estimated soil-water partition coefficients (K_{oc}) is reported above and indicates that sorption of chloroform to soil/sediments and dissolved organic material will occur. Pavlou (1980) estimates that sorption of volatile organic compounds will range from low to moderate. The combined high water solubility and low organic partitioning of chloroform suggest that this compound will exhibit a high degree of environmental mobility.

Studies with marine organisms provide evidence for only weak to moderate bioaccumulation of chloroform. A range of estimated bioconcentration factors (BCFs) for chloroform is also presented above. ASTM (1985) indicates that chemicals with bioconcentration factors less than approximately 100 have low potential for causing harm to wildlife and human health via biomagnification of residues up food chains. The magnitude of the concentration factors suggest that appreciable bioconcentration or biomagnification of chloroform residues is not likely to occur.

Health Effects

Humans may be exposed to chloroform by inhalation, ingestion, or skin contact. Chloroform has been detected in 99.5% of U.S. finished drinking water samples. (ATSDR, 1989) Typical concentrations are in the range of 32-68 ug/L and typical water intakes are calculated to be 64 to 132 ug/person/day. (ATSDR, 1989) "There are no epidemiologic studies on chloroform itself. ... Several ecological and case-control studies of populations consuming chlorinated drinking water in which chloroform was the major chlorinated organic show small significant increases in the risk of rectal, bladder or colon cancer on an intermittent basis. Many other suspected carcinogens were also present in these water supplies." (USEPA, 1989). "Although it

can be concluded that the human data suggest a possible increased risk of cancer at these three sites because chloroform is the predominant trihalomethane in drinking water, the data are too weak to draw a conclusion about the carcinogenic potential of chloroform." (ATSDR, 1989 citing EPA 1985)

Other toxic effects include local irritation of the eyes, central nervous system depression, gastrointestinal irritation, liver and kidney damage, cardiac arrythmia, ventricular tachycardia and bradycardia. Death from chloroform overdosing can occur and is attributed to ventricular fibrillation. Chloroform anesthesia can produce delayed death as a result of liver necrosis.

In laboratory animals, exposure to chloroform by inhalation,intragastric administration, or intraperitoneal injections produces liver and kidney damage. Chronic administration of chloroform by gavage is reported to produce a dose-related increase in the incidence of kidney epithelial tumors in rats and a dose-related increase in the incidence of hepatocellular carcinomas in mice (IARC 1979, USEPA 1980). Based on EPA's Proposed Carcinogen Risk Assessment Guidelines, chloroform is classified in EPA's Group B2 (probable human carcinogen) based upon sufficient evidence of carcinogenicity in animals and inadequate epidemiological evidence (USEPA 1985b).

An increased incidence of fetal abnormalities was reported in offspring of pregnant rats exposed to chloroform by inhalation at levels of 100 and 300 ppm, with 30 ppm being a no effect level. Oral doses of chloroform that caused maternal toxicity produced relatively mild fetal toxicity in the form of reduced birth weights. There are limited data suggesting that chloroform has mutagenic activity in some test systems. However, negative results have been reported for bacterial mutagenesis assays.

The oral LD_{50} and inhalation LC_{Lo} values for chloroform in the rat are 908 mg/kg and 39,000 mg/m^3 per 4 hours, respectively (ACGIH 1980).

Toxicity to Wildlife and Domestic Animals

Limited information is available concerning the toxicity of chloroform to organisms exposed at known concentrations (USEPA 1980). Median effect concentrations for two freshwater and one invertebrate species range from 28,900 to 115,000 ug/liter. Twenty-seven day LC5O values of 2,030 and 1,240 ug/liter were reported for embryo-larval tests with rainbow trouts in water at two levels of hardness. The only reliable result concerning the toxicity of chloroform to saltwater aquatic life is a 96-hour LC_{50} value of 81,5000 ug/liter for pink shrimp.

No data were collected on the toxicity of chloroform to wild domestic animals in the literature reviewed. Conceivably, acute effects on wildlife can occur in the vicinity of a major chloroform spill, however, chronic effects from long term exposure to low ambient levels is unlikely (USEPA 1985b).

Regulations and Standards

Ambient Water Quality Criteria (USEPA 1986):

The available data are not adequate for establishing criteria. However, EPA does report the lowest values known to be toxic in freshwater aquatic organisms.

Aquatic Life (Freshwater)

Acute Toxicity: 28,900 ug/liter
Chronic Toxicity: 1,240 ug/liter

Human Health

Due to the carcinogenicity of chloroform the ambient water criterion is set at zero. However, estimates of the carcinogenic risks associated with lifetime exposure from the ingestion of contaminated water and contaminated aquatic organisms are:

Risk	Concentration
10^{-5}	1.90 ug/liter
10^{-6}	0.19 ug/liter
10^{-7}	0.019 ug/liter

CAG Potency Slope for oral exposure (USEPA 1989):
6.1×10^{-3} mg/kg/day^{-1}

The CAG oral potency slope is derived from the rat drinking water study in which the 2 high doses but not the 2 low doses caused an increase in kidney epithelial tumors.

Shell risk assessment: MLE potency from multistage model using the drinking water study and adjusting for differences in percent of dose metabolized yields a potency of 1.2×10^{-4} mg/kg/day-1. The geometric mean of 5 low-dose extrapolation models estimates a potency of 1.4×10^{-2} (mg/kg/day)$^{-1}$. The Shell estimated potency is applicable to both oral and inhalation routes of exposure.

In the case of chloroform it is plausible to consider the MLE estimate and the geometric mean of all models since the experiment: 1. was designed to detect low dose tumorigenic response and 2. the route and rate of chemical administration (drinking water) more closely mimics human exposure as compared to pulse gavage dosing used in the other studies. Even though the 2 low dose groups (400 ppm and 200 ppm) contained 148 and 313 animals respectively, there was no increase in kidney tumors. Thus a higher level of confidence, less uncertainty, can be attached to these estim (Shell, 1988) The third reason for considering the alternative dose-response m s is the lack of genotoxicity and distinct possibility of phosgene induced cytotoxicity. " The overwhelmingly negative nature of the results from multiple laboratories in a spectrum of in-vitro, in vivo, prokaryotic and eukaryotic test systems strongly suggests that chloroform is either not genotoxic or very weakly positive (Shell, 1988) or .." may be mutagenic, but no definitive conclusion can be reached concerning mutagenicity of chloroform" ATSDR, 1989. Chloroform may be acting through a threshold like mechanism involving cytotoxicity due to the phosgene metabolite.

The inhalation potency value is based on the geometric mean of the linearized multistage risk estimates derived from male and female mouse studies in which chloroform was mixed in corn oil and administered to the mice in daily pulse doses using a stomach tube (gavage). The tumor response (mouse liver tumors) was 80% and 95% in the 2 female groups which is near a maximal response which yields little dose-response information that is useful in high dose to low dose extrapolation. On the other hand the dosage rates were lowered in the male mice such that the liver tumor response was 35% in the low dose and 98% in the high dose. The CAG potency slope is based on the geometric mean of the male (3.3×10^{-2}) and female (2.0×10^{-1}) upper bound potencies calculated from the linearized multistage model. However, from a data quality viewpoint the near maximum response in the females

makes that data set less reliable for low dose extrapolation. For comparison the 10^{-4} risk dose using the male data is 0.003 mg/kg while the female potency predicts a 10^{-4} risk dose of 0.0005 mg/kg or 6 times smaller.

EPA argued that since there were no inhalation studies and no pharmacokinetic data to contraindicate the use of the gavage data therefore it was appropriate to use the mouse gavage data to derive the inhalation route potency. The agency is silent on the question of why the drinking water studies were not used since intake over a period of time as occurs with drinking water more closely approximates expected typical inhalation exposure for the general population. If the tumor incidence versus dose is plotted for the rat chloroform in corn oil gavage study with the same data for the rat drinking water study, it is noted that the tumor response in the gavage with corn oil is about 30% higher than at comparable doses in the drinking water study.

CAG Potency Slope for inhalation exposure (USEPA 1989):
8.1 x 10-2/ mg/kg/day

Primary Drinking Water Standard (MCL): 0.10 mg/liter (total trihalomethanes) (40 CFR 141.12).

NIOSH recommended Standard: Ceiling = 9.8 mg/m^3 (1 hr)

OSHA Standard: Ceiling = 244 mg/m^3

ACGIH: STEL[1] = 50 mg/m^3

Oral RfD = .01 mg/kg/day (USEPA, 1989, IRIS)
= (ACTUALLY 0.0129 MG/KG FROM RAW DATA)

[1] Short term Exposure Limit

RANGE OF D_T ValueS

The D_T value is defined as that contaminant intake rate (mg/kg/day) that should not induce an adverse effect to human health or should not pose a risk of cancer occurrence greater than a predetermined risk level.

A range of DTs are developed which reflect the certainty and uncertainty in the underlying toxicology and relevance to man. There is considerable information on the effects and lack of effects of chloroform in humans that time did not permit fully integrating into this analysis. The extensive human experience with chloroform has the effect of reducing the uncertainty. A number of past pharmaceutical products have contained chloroform. ATSDR (1989) cites one study in which liver function tests were normal in a population ingesting between 68 and 197 mg chloroform per day. The upper value will be used as one bench mark for evaluation of appropriateness of exposure limits. A second bench mark is based on the workplace experience reported by Challen et al. (1958) (cited by ATSDR, 1989) in which liver function tests were normal in a population breathing 22 to 71 ppm. At the high level (77 ppm, 385 mg/M3) a 2 hour/day exposure (1.25 M^3/hour) would result in an inhaled dose of 963 mg or about 1 gram/day.

For carcinogens such as chloroform, one D_T value is based on the USEPA Cancer Assessment Group's cancer potency slopes. The cancer potency slope for chloroform for oral exposure routes is based on a rat drinking water study and for inhalation exposure is based on a mouse oral pulse dosing gavage study. The slopes are intended to be a plausible upper bound of the potency of a carcinogen in inducing cancer at low doses. Calculation of a D_T using a cancer potency slope requires selection of an acceptable cancer risk level. A range of risk levels from 10^{-4} to 10^{-7} is considered for all carcinogens, therefore a range of D_T values is presented. Derivation of the oral D_T values for chloroform is as follows:

$$D_T = \frac{\text{Risk Level}}{\text{Potency Slope (mg/kg/day)}^{-1}}$$

$$= \frac{1 \times 10^{-4}}{6.1 \times 10^{-3} \text{ (mg/kg/day)}^{-1}}$$

$$= 1.6 \times 10^{-2} \text{ mg/kg/day}$$

The inhalation D_T values for chloroform were similarly computed using the inhalation potency slope.

The range of CAG cancer potency based D_T values for chloroform is presented below:

Risk Level	D_T Oral Exposure (mg/kg/day)	D_T Inhalation Exposure (mg/kg/day)
10^{-4}	1.6×10^{-2}	1.2×10^{-3}
10^{-5}	1.6×10^{-3}	1.2×10^{-4}
10^{-6}	1.6×10^{-4}	1.2×10^{-5}

A corresponding second set of DT values derived from the MLE estimate from the multistage model (Shell, 1988) and the geometric mean of 5 plausible dose-response models are:

Risk Level	MLE based (mg/kg/day)	Geometric Mean Based (mg/kg/day)
10^{-4}	8×10^{-1}	$7 \times 10^{+1}$
10^{-5}	8×10^{-2}	7×10^{0}
10^{-6}	8×10^{-3}	7×10^{-1}

The difference in the DT based on the CAG potency and the MLE estimate of potency is 50. The geometric mean based DT predicts a 4000 fold higher safe dose than the CAG based DT.

The third D_T is based on the EPA RfD which in turn is based on protecting against liver effects in dogs which are the most sensitive known species with effects demonstrated after 7.5 years of exposure to 15 mg/kg for 6 days/week and is 0.01 mg/kg. A 1000 fold safety factor was used since the lowest dose used (15 mg/kg) produced some effects. At the third D_T of 0.01 mg/kg the total dose in a 70 kg human would be 0.7 mg/day. Recalling the 2 bench mark doses developed above (197 and 960 mg/day) the dog derived RfD would appear to provide an apply margin of safety (197/.7 = 281). A D_T based on preventing liver damage should be given some weigh since chloroform may be acting through a non-genotoxic mechanism and the carcinogenicity may be linked to the overt cell damage that can be seen at the higher doses associated with liver tumors in mice and kidney tumors in rats (see ATSDR, 1989 for details) The third DT based on a 1000 fold safety factor is smaller than the 10-4 and 10-5 risk based doses estimated by the MLE of the multistage model.

The fourth D_T is based on using a smaller safety factor given the long term human experience with chloroform. Using the same end point of liver damage in dogs, but a safety factor of 100 yields a D_T = 0.129 mg/kg or for a 70 kg human a daily exposure of 9 mg which is still smaller than the 2 no-effect bench mark doses developed above. This increases the certainty that a D_T of 0.129 mg/kg is still protective against demonstrable liver toxicity.

CERTAINTY AND UNCERTAINTY IN THE D_T VALUES AND UNDERLYING TOXICOLOGY

Chloroform is a carcinogen in rats and mice when given in sufficient amounts. Chloroform is not a potent genotoxin and if it is genotoxic at all it appears to be a weak genotoxin. The human epidemiology data does not lead to the conclusion that chloroform is a carcinogen in people.

The question of whether or not chloroform is a human carcinogen, especially at low doses, can not be answered by science at this point in time. The question of carcinogenicity of chloroform for humans contains at least 3 major factors: 1. is chloroform carcinogenic at any dose in humans? 2. Is chloroform as potent a carcinogen at low doses as predicted by the animal data? and 3. If chloroform is a human carcinogen, is the carcinogenicity related to overt tissue damage as occurs with the higher levels of chloroform exposure? Based on the work place standard of 10 ppm (50 mg/M^3) a 8 hour/day (10M3) exposure results in a calculated dose of 7 mg/kg. This exposure rate for 40 years, 5 days/ week would result in a predicted cancer risk of 1 in 4 (0.23, rounded). If the exposure is overestimated by a factor of 2 the risk is 1 in 8 and so on. For a daily intake of 200 mg (pharmaceutical products for example) then the lifetime risk at the rat based oral potency number predicts a risk of 1 in 58. This suggests that either/and 1.the potency is over estimated for low doses, 2. a chloroform cancer problem has went undetected or 3. the actual human exposures were much less.

If chloroform acts through some cancer mechanism associated with measurable cell damage then a D_T that is protective for tissue damage would be protective against a cancer risk. This is supported in part by the generally negative genotoxicity assays with the caveat that the assays may not have been done with adequate levels of enzyme systems to produce high enough levels of active metabolites.

The certainties are 1. chloroform causes liver and kidney tumors in laboratory animals at doses and in tissues where visible tissue damage occurs before tumors occur. 2. Chloroform at sufficient dosages is toxic in animals and humans. 3. Humans have come into extensive contact with chloroform over the years and there is no significant substantial evidence that chloroform is a human carcinogen at typical levels of exposure. 4. There is circumstantial evidence confounded by the presence of multiple materials that exposures to mixtures containing chloroform that there is a tumorigenic response in human

REFERENCES

ASTM. 1985. Standard Practice for Conducting Bioconcentration Tests with Fishes and Saltwater Bivalve Mollusca. Designation E 1022-84, pages 590-62. In: 1985 Annual Book of ASTM Standards Volume 11.04. American Society for Testing and Materials, Philadelphia, Pennsylvania.

ATSDR (1989) Agency for Toxic Substances and Disease Registry. Toxicology Profile for Chloroform.

AMERICAN CONFERENCE OF GOVERNMENTAL AND INDUSTRIAL HYGIENISTS (ACGIH) 1980. Documentation of the Threshold Limit Values. 4th ed. Cincinnati, Ohio.

DAVIES, R.P. and A.J. DOBBS. 1984. The prediction of bioconcentration in Fish. Water Res. 18(10): 1253-1262.

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC). 1979. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. Vol. 20: Some Halogenated Hydrocarbons. World Health Organization, Lyon, France. Pp. 408-415.

KADEG, R.D. , S.P. PAVLOU, and A.S. DUXBURY. 1986. Elaboration of Sediment Normalization Theory for Non Polar Hydrophobic Chemicals. U.S. Environmental Protection Agency, Criteria and Standards Division, Washington D.C.

LYMAN, W.J. and C.P. LORETI. 1987. Prediction of Soil and Sediment Sorption for Organic Compounds. Final Report. U.S. Environmental Protection Agency, Monitoring and Data Support Division, Office of Water Regulations

and Standards. Washington D.C.

LYMAN, W.J., W.F. REEHL and D.H. ROSENBLADT. 1982. Handbook of Chemical Property Estimation Methods: Environmental Behavior of Organic Compounds. McGraw-Hill Book Co., New York.

MORIGUCHI, I. 1975. Quantitative Structure-Activity Studies. I. Parameters Relating to Hydrophobicity. Chem. Pharmacol. Bull. 23(2):247-257.

NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH (NIOSH). 1982. Registry of Toxic Effects of Chemical Substances. Volumes I-III. U.S. Department of Health and Human Services. Cincinnati, OH.

PAVLOU, S.P. 1980. Thermodynamic Aspects of Equilibrium Sorption of Persistent Organic Molecules at the Sediment-Seawater Interface: A Framework For Predicting Distributions in the Aquatic Environment. IN: Contaminants and Sediments. Volume 2. Baker, R.A. (Editor). Science Publishers, Inc. Ann Arbor, MI.

PERRY, R.H. and C.H. CHILTON. 1973. Chemical Engineer's Handbook, 5th. Edition. McGraw-Hill Book Co., New York, NY.

SABLJIC, A. 1984. Predictions of the Nature and Strength of Soil Sorption of Organic Pollutants by Molecular Topology. J. Agric. Food Chem. 32 :243-246.

SAX, N.I. 1975. Dangerous Properties of Industrial Materials. 4th ed. Van Nostrand Reinhold Co., New York.

SHELL (1988). Chloroform Risk Evaluation Document. Rocky Mountain Arsenal.

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). 1979. Water-Related Environmental Fate of 129 Priority Pollutants. Washington, D.C. December 1979. EPA 440/4-79-029.

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). 1980. Ambient Water Quality Criteria for Chloroform. Office of Water Regulations and Standards, Criteria and Standards Division, Washington, D.C. October 1980. EPA 440/5-80-033.

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). 1984. Health Effects Assessment for Chloroform. Environmental Criteria and Assessment Office, Cincinnati Ohio. September 1984. ECAO-CIN-HO1O (Final Draft).

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). 1985a. Draft Superfund Public Health Evaluation Manual. Prepared by: ICF Incorporated, Washington D.C. USEPA Office of Solid Waste and Emergency Response, Washington D.C. EPA Contract No. 68-01-7090.

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). 1985b. Health Assessment Document for Chloroform. Final Report. Office of Health and Environmental Assessment, Washington, D.C. September 1985. EPA 600/8-84/004F.

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). 1986. Quality Criteria for Water, 1986 ("The Gold Book"). Office of Water Regulations and Standards, Washington, D.C. EPA 440/5-86-001.

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). 1989. Integrated Risk Information System (IRIS). Access Date: June 27, 1989. [Note: This is a computerized data base.]

VALVANI, S.C. , S.H. YALKOHSKY, and T.J. ROSEMAN. 1980. Solubility and Partitioning. IV. Aqueous Solubility and Octanol-Water Partition Coefficients of Liquid Nonelectrolytes. J. Pharm. Sci. 70(5):502-202.

WEAST, R.E., ed. 1981. Handbook of Chemistry and Physics. 62nd ed. CRC Press, Cleveland, Ohio.

DDT/DDD/DDE

Summary

DDT, 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane, was one of the most widely used agricultural crop pesticides in the United States until it was banned for all but essential public health uses on January 1, 1973. It is still used worldwide today, primarily for the control of insect vectors that carry malaria-causing parasites. As a result of its extensive use in the United States from 1946-1972 and its environmental persistence, DDT is a ubiquitous soil, air, water, and food contaminant. DDD, 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene, and DDE, 1,1-dichloro-2,2-bis(p-chlorophenyl)ethane, persist as the primary human metabolites of DDT, the environmental degradation products of DDT, and as contaminants in technical grade DDT. Like DDT, DDD has also been used as a pesticide. The high lipid solubility and environmental persistence of DDT, DDD, and DDE have resulted in their bioaccumulation in food chain organisms. Bioaccumulation and subsequent biomagnification processes are responsible for the decreased reproductive success of many bird species.

DDT, DDD, and DDE have been shown to be carcinogenic in mice, causing liver tumors, and also have been positively associated with an increased incidence of lung tumors (DDT, DDD) and malignant lymphomas (DDT) in mice. DDT has been positively associated with cancer of the liver, lung, and adrenal glands in rats, while administration of DDD and DDE to rats, has been associated with an increased incidence of thyroid tumors. DDE has also been positively associated with an increased incidence of liver tumors in hamsters. Data as to the carcinogenicity of DDT, DDD, or DDE in humans are conflicting and insufficient. Central nervous system effects in humans following acute exposure include headache, nausea, fatigue, dizziness, uncertain gait, hypersensitivity to contact, vomiting, and convulsions. A number of in vitro and in vivo assays have shown that DDT, DDD, and DDE are genotoxic.

Reported concentrations of DDT and DDE in United States air samples range from 1.4 to 1560 ng/m^3 and 1.9 to 131 ng/m^3, respectively. A maximum air concentration of 33.3 ng/m^3 for DDD has been reported. Surface water samples have contained levels of DDT, DDD, and DDE in concentrations ranging from 0.005 to 0.316 μg/l, 0.015 to 0.840 μg/l, and 0.02 to 0.05 μg/l, respectively. A five-city survey of soil samples reported a DDT concentration range of 0.01 to 5.86 ppm and a DDD concentration range of 0.01 to 39 ppm. Soil monitoring in areas in which DDT application was extensive has shown that over time the ratio of DDE:DDT increases, suggesting a transformation of DDT to DDE.

Most recent market basket surveys report the presence of DDT in leafy vegetables at a concentration of 0.4 ppb and in root vegetables at a concentration of 0.6 ppb, while DDE has been reported to be present in a number of items including concentrations of 4.6 ppb in root vegetables, 3.0 ppb in meat, fish, and poultry, 2.4 ppb in leafy vegetables, and 1.5 ppb in dairy products. Average dietary intake of DDT and DDE was estimated to be 0.0022 mg/day for the year 1981.

Technical DDT is a mixture containing 65-80 percent, p,p'-DDT, 15-20 percent o,p'-DDT, up to 4 percent p,p'-DDD, and traces of other materials. Metabolites of DDT include p,p'-DDE and o,p'-DDD. The DDT isomers and metabolites are usually found together and generally have similar properties; therefore, they are considered together. Where differences occur, the specific isomer is identified. DDT is used to refer to the combination of technical material and metabolites. Specific DDT isomers are identified as such.

CAS Number:	p,p'-DDT:	50-29-3
	o,p'-DDT:	789-02-6
	p,p'-DDD:	72-54-8
	o,p'-DDD:	53-19-0
	p,p'-DDE:	72-55-9

Chemical Formula:	p,p'- and o,p'-DDT:	$C_{14}H_9Cl_5$
	p,p'- and o,p'-DDD:	$C_{13}H_{10}Cl_4$
	p,p'- and o,p'-DDE:	$C_{14}H_8Cl_4$

IUPAC Name:	p,p'-DDT:	1,1,1-Trichloro-2,2-bis(4-chlorophenyl) ethane
	o,p'-DDT:	1,1,1-Trichloro-2-(2-chlorophenyl)-2-(4-chlorophenyl)ethane
	p,p'-DDD:	1,1-Dichloro-2,2-bis(4-chlorophenyl)ethane
	o,p'-DDE:	1,1-Dichloro-2,2-bis(4-chlorophenyl)ethane

Important Synonyms and Trade Names:

DDT:	Dichlorodiphenyltrichloroethane, dicophane, chlorophenotane, Gesarol, Neocid
p,p'-DDD:	TDE, Rothane

Chemical and Physical Properties

Molecular Weight:	o,p'- and p,p'-	DDT:	354.5
		DDD:	320
		DDE:	318

Boiling Point: DDT: 260°C

Melting Point: DDT: 109°C
DDD: 112°C
DDE: 90°C
88.4°C (Burrows et al. 1979)

Solubility in Water:	p,p'-	DDT:	5.5 µg/liter
	o,p'-	DDT:	26 µg/liter
	p,p'-	DDD:	20 µg/liter
		DDE:	14 µg/liter

Solubility in Organics: DDT: Soluble in acetone, benzene, cyclohexanone, morpholine, pyridine, and dioxane

Log Octanol/Water Partition Coefficient (K_{ow}):

DDT:	3.98-6.19 (Cited in Hansch and Leo 1979)
	5.98 (Kenaga 1980)
	6.19 (Rao and Davidson 1983)
	6.36 (Davies and Dobbs 1984)
	5.98 (Lyman et al. 1982)
	5.98; 6.19; 6.28; 6.36 (Geyer et al. 1984)
	4.0-7.48 (Kadeg et al. 1986. Range and geometric mean of 20 literature values) (geometric mean = 6.07)

p,p'-	DDT:	3.98
p,p'-	DDD:	5.99
o,p'-	DDD:	6.08
	DDE:	5.69 (Rao and Davidson 1983)
		5.60 (Kadeg et al. 1986)
		7.00 (USEPA 1986a)

Soil/Water Partition Coefficient (K_{oc}):

p,p'-DDE:

50,100	Sabljic (1984) (experimental)
147,900	Kadeg et al. (1986) literature value
19,350; 662,200	Kadeg et al. (1986) (log K_{ow} = 4.86, 7.0)
10,490; 153,100	Lyman et al. (1982) Eqn 4-8 (log K_{ow} = 4.86, 7.0)
17,620; 818,500	Lyman and Loreti (1987) (log K_{ow} = 4.86; 7.0)
4,400,000	USEPA (1986a)

p,p'-DDT:

23,800	Kenaga (1980) (experimental)
140,000	Chiou et al. (1979) (experimental)
243,000	Rao and Davidson (1983)
4×10^{-6} - 43,650	Kadeg et al. (1986) (Range and geometric mean
(geometric mean = 302,000)	of 17 literature values)

Bioconcentration Factor:

p,p'-DDE:

13,900	Lyman et al. (1982) Eqn 5-2 (log K_{ow} = 7.07)
12,430	Lyman et al. (1982) Eqn 5-2 (log K_{ow} = 5.69)
2,043	Davies and Dobbs (1984) Eqn A (S = 0.12)
25,362	Davies and Dobbs (1984) Eqn B (log K_{ow} = 7.07)
980	Davies and Dobbs (1984) Eqn C (log K_{ow} = 5.60)
3,400	Davies and Dobbs (1984) Eqn B (log K_{ow} = 5.60)
10,600	Lyman et al. (1982) Eqn 5-2 (log K_{ow} = 5.60)
100,000	Davies and Dobbs (1984) (experimental)
366-9,659	Davies and Dobbs (1984) Eqn B (log K_{ow} = 3.98-6.36)

p,p'-DDT:

61,600; 84,500	Kenaga (1980) Table 3 (experimental)
623 - 29,800	Lyman et al. (1982) Eqn 5-2 (log K_{ow} = 3.98-6.19)
20,600	Lyman et al. (1982) Eqn 5-2 (log K_{ow} = 5.98)
40,100	Lyman et al. (1982) Eqn 5-2 (log K_{ow} = 6.36)
27,436 - 13,913	Davies and Dobbs (1984) Eqn A (s = 0.0012 - 0.004)
1,710	Davies and Dobbs (1984) Eqn C (log K_{ow} = 6.07)
6,483	Davies and Dobbs (1984) Eqn B (log K_{ow} = 6.07)
24,200	Lyman et al. (1982) Eqn 5-2 (log K_{ow} = 6.07)

Vapor Pressure:

p,p'- DDT:	1.9×10^{-7} mm Hg at 25°C
p,p'- DDT:	7.3×10^{-7} mm Hg at 30°C
o,p'- DDT:	5.5×10^{-6} mm Hg at 30°C
p,p'- DDD:	1.0×10^{-6} mm Hg at 30°C
o,p'- DDD:	1.9×10^{-6} mm Hg at 30°C

DDE: 6.5×10^{-6} mm Hg at 20°C (USEPA 1979)

Henry's Law Constant:

DDD: 7.96×10^{-6} atm-m^3/mole (USEPA 1985)

DDE: 1.1×10^{-4} atm-m^3/mole (calculated)
6.8×10^{-5} atm-m^3/mole (USEPA 1985)
2.86×10^{-3} Dimensionless

DDT: 9×10^{-5} atm-m^3/mole (calculated)
5.13×10^{-4} atm-m^3/mole (USEPA 1985)
2.16×10^{-2} Dimensionless

Transport and Fate

DDT and its metabolites are very persistent in the environment. Volatilization is not likely to be an important transport process from soil and water for DDT and its metabolites as evidenced by their low vapor pressures. The half-life of DDT in the atmosphere is not certain, however, it is lost from the atmosphere by rain and photochemical degradation (USEPA 1984).

The range of the soil-water partition coefficients (K_{oc}) reported above indicates that sorption of DDT and its metabolites to soils/sediments and dissolved organic material will occur. Pavlou (1980) estimates that sorption of chlorinated hydrocarbon pesticides is very high. The combined low water solubility and high organic partitioning suggest that DDT will exhibit little environmental mobility. The half-life of DDT in soil is estimated to range between 3 and 15 years (USEPA 1984).

Although it occurs slowly, p,p'-DDT, o,p'-DDT, and DDD are ultimately biotransformed in the environment (microorganisms) to form bis(2-chlorophenyl) methanone (DDCO). In aquatic environments, indirect photolysis may also be important for p,p'-DDT and o,p'-DDT. For DDE, direct photolysis is a more

important fate process in the environment, although biotransformation may also be important.

A range of experimental and estimated bioconcentration factors (BCFs) for DDT and its metabolites in fish is reported above. Biomagnification of DDT and its metabolites has been demonstrated in many species, most notably in raptors. ASTM (1985) indicates that chemicals with bioconcentration factors less than approximately 100 have low potential for causing harm to wildlife and human health via magnification of residues up food chains. The magnitude of the concentration factors indicates that significant bioconcentration and biomagnification of DDT residues can occur.

Health Effects

Human exposure to DDT, DDD, and DDE can occur through inhalation, ingestion, or dermal contact. Human absorption of DDT is directly proportional to dietary exposure with a half-life clearance of between 10 and 20 years (U.S. EPA 1988). Epidemiological studies of human exposure to DDT have either been of insufficient duration or presented conflicting results to show evidence of a relationship between DDT and human cancer. "Autopsy studies relating tissue levels of DDT to cancer incidence have yielded conflicting results. Three studies reported that tissue levels of DDT and DDE were higher in cancer victims than in those dying of other diseases...In other studies no such relationship was seen...Studies of occupationally exposed workers and volunteers have been of insufficient duration to be useful in assessment of the carcinogenicity of DDT to humans." (U.S. EPA 1988) Human epidemiological data are not available for DDD or DDE (U.S. EPA 1989a, 1989b).

Occupational studies of workers employed in pesticide manufacturing show that DDT stimulates hepatic enzyme activity, although no direct evidence of human liver dysfunction has been reported (ATSDR 1988). The central nervous system appears to be the primary target for acute human exposures to DDT. "Clinical symptoms include hyperexcitability, tremors, and convulsions." (ATSDR 1988) These

symptoms appear to be reversible upon cessation of exposure (ATSDR 1988). Chromosomal aberrations have been reported in human lymphocytes upon in vitro exposure to DDT, as well as in plasma of workers occupationally exposed to DDT (ATSDR 1988). Although there are no data to suggest that maternal DDT exposure is associated with adverse human reproductive outcomes, DDT, DDD, and DDE have been found in human blood, placental tissue, and umbilical cord blood (ATSDR 1988).

There are a number of animal studies that confirm the carcinogenicity of DDT, DDD, and DDE. Liver tumors have been reported in several strains of mice and rats upon dietary exposure to DDT, in mice upon dietary exposure to DDD, and in mice and hamsters upon dietary exposure to DDE (ATSDR 1988, U.S. EPA 1988, 1989a, 1989b). Lung adenomas have been reported in mice exposed to DDT via diet or gavage and to mice exposed to dietary DDD (ATSDR 1988, U.S. EPA 1989a). Malignant lymphomas were also reported for mice orally exposed to DDT (ATSDR 1988). Bioassay data also suggest that DDD and DDE induce thyroid follicular cell tumors in rats upon dietary exposure (U.S. EPA 1989a, 1989b). DDT has also been reported to be a liver tumor promoter in rat studies (U.S. EPA 1988). Chromosomal damage has also been reported in Chinese hamster cells following exposure to DDT, DDD, or DDE and in the bone marrow of mice upon in vivo exposure to DDT (ATSDR 1988). DDT and DDD have been positive in several other in vitro and in vivo genotoxicity assays (ATSDR 1988). EPA has classified DDT, DDD, and DDE as Probable Human Carcinogens (B2) (U.S. EPA 1989a, 1989b). The International Agency For Research on Cancer has classified DDT as Group 2B: evidence for carcinogenicity to humans is inadequate but evidence for carcinogenicity to animals is sufficient.

Other animal data show the liver to be one of the primary target organs of non-carcinogenic DDT toxicity. Chronic dietary exposure to DDT has resulted in a number of hepatic effects including increased enzyme activity, increased liver weight, necrosis, hypertrophy, and hyperplasia in rats, hamsters and dogs (ATSDR 1988, U.S. EPA 1988). Chronic dietary exposure to DDE has also resulted in necrosis of

the liver in hamsters (ATSDR 1988). Animal studies have confirmed the central nervous system effects reported in humans upon exposure to DDT. Acute oral exposure to DDT has resulted in tremors, myoclonus, hyperexcitability, and convulsions in rats and mice, while chronic exposure has been associated with tremors and general hyperirritability in rats (ATSDR 1988). Exposures to DDT, DDD, or DDE have been associated with a number of adverse developmental or reproductive outcomes in various animal species upon maternal oral exposure. These effects include embryotoxicity and fetotoxicity, as well as reduced fertility in experimental animals in the absence of maternal toxicity (ATSDR 1988). Data from studies in mice, rats, and rabbits also indicate that oral exposure to DDT induces a humoral response including increases in immunoglobulins (ATSDR 1988).

Various LD_{50} values have been reported for DDT and its metabolites. Oral LD_{50} values for DDT ranged from 113 to 800 mg/kg for rats and were 400 and 300 mg/kg for guinea pigs and rabbits, respectively (ATSDR 1988). Oral LD_{50}s were reported to range from 400 to 4,000 mg/kg for rats and 1,466 to 1,507 mg/kg for mice exposed to DDD (ATSDR 1988). The LD_{50}s for rats upon intraperitoneal and subcutaneous injections of DDT were reported to be 9.1 and 1,500 mg/kg, respectively. The LD_{50} range in mice exposed to DDT via intraperitoneal injection was reported to be 32 to 333 mg/kg (ATSDR 1988).

Toxicity to Wildlife and Domestic Animals

DDT has been extensively studied in freshwater invertebrates and fishes and is quite toxic to most species. The range of toxicities to these organisms was 0.18 to 1,800 μg/liter and the freshwater final acute value for DDT and its isomers was determined by EPA to be 1.1 μg/liter (USEPA 1980). Saltwater species were somewhat more sensitive to DDT. The saltwater final acute value for the DDT isomers was 0.13 μg/liter (USEPA 1980). Only one chronic toxicity test on aquatic species was reported. This test indicated that the acute-chronic ratio for DDT may be

high (65 in the reported study), but the data were insufficient to allow calculation of a final acute-chronic ratio.

DDT, DDD, DDE and other persistent organochlorine pesticides are primarily responsible for decreases in the reproductive capabilities and consequently in the populations of some fish-eating birds; particularly the bald eagle, brown pelican, and osprey. DDT has also been shown to significantly decrease populations of other species of waterbirds, raptors, and passerines (EOP 1971).

Regulations and Standards

Ambient Water Quality Criteria (USEPA 1986b):

Aquatic Life (Freshwater)

DDT:

Acute toxicity:	1.1 μg/liter (at any time)
Chronic toxicity:	0.001 μg/liter (24-hour average)

Aquatic Life (Marine)

Acute toxicity :	0.13 μg/liter (at any time)
Chronic toxicity:	0.001 μg/liter (24-hour average)

DDD and DDE: The available data are not adequate for establishing Ambient Water Quality Criteria. However, EPA (U.S. EPA 1986b) does report the lowest values known to be toxic in aquatic organisms.

Aquatic Life (Freshwater)

Acute toxicity:	DDD: 0.06 μg/liter DDE: 1050 μg/liter
Chronic toxicity	DDD and DDE: No available data

Aquatic Life (Marine)

Acute toxicity: DDD: 3.6 μg/liter
DDE: 14 μg/liter

Chronic toxicity: DDD and DDE: No available data

Human Health - Carcinogenicity

DDT

Due to the carcinogenicity of DDT and its isomers the ambient water criterion is set at zero. However, U.S. EPA (1988) estimates of the carcinogenic risks associated with lifetime exposure from consumption of water are:

Risk	Concentration
10^{-4}	10 μg/L
10^{-5}	1 μg/L
10^{-6}	0.1 μg/L

Drinking Water Unit Risk (USEPA 1988): 9.7E-6 $(\mu g/L)^{-1}$

CAG Potency Slope for Oral Exposure (USEPA 1988): 0.34 $(mg/kg/day)^{-1}$

USEPA (1988) notes that if the water concentration exceeds 1,000 μg/L the unit risk factor cited above should not be used because above this concentration the slope factor may differ from that stated.

CAG Potency slope for inhalation exposure (USEPA 1988): 0.34 $(mg/kg/day)^{-1}$

Inhalation Unit Risk (USEPA 1988): 9.75E-5 $(\mu g/m^3)^{-1}$

Air Concentrations at Specified Risk Levels:

Risk	Concentration
10^{-4}	1 $\mu g/m^3$
10^{-5}	0.1 $\mu g/m^3$
10^{-6}	0.01 $\mu g/m^3$

USEPA (1988) notes that if the air concentration exceeds 100 $\mu g/m^3$, the unit risk factor cited above should not be used because above this concentration, the slope factor may differ.

DDD

CAG Potency Slope for Oral Exposure (USEPA 1989a): 0.24 $(mg/kg/day)^{-1}$

Drinking Water Unit Risk (USEPA 1989a): 6.96E-6 $(\mu g/L)^{-1}$

Drinking Water Concentrations at Specified Risk Levels:

Risk	Concentration
10^{-4}	10 $\mu g/L$
10^{-5}	1 $\mu g/L$
10^{-6}	0.1 $\mu g/L$

USEPA (1989a) notes that if the water concentration exceeds 1,000 $\mu g/L$, the unit risk factor cited above should not be used because above this concentration, the slope factor may differ.

DDE

CAG Potency Slope for Oral Exposure (USEPA 1989b): 0.34 $(mg/kg/day)^{-1}$

Drinking Water Unit Risk (USEPA 1989b): 9.7E-6 $(\mu g/L)^{-1}$

Drinking Water Concentrations at Specified Risk Levels:

Risk	Concentration
10^{-4}	10 μg/L
10^{-5}	1 μg/L
10^{-6}	0.1 μg/L

USEPA (1989b) notes that if the water concentration exceeds 1,000 μg/L, the unit risk factor cited above should not be used because above this concentration, the slope factor may differ from that stated.

Human Health- Non-Carcinogenic Endpoints

USEPA (1988) has issued an oral reference dose value for DDT assuming that a threshold level exists for other toxic effects, such as cellular necrosis of the liver, at which this effect would not occur in humans exposed to DDT on a daily basis.

Oral RfD for DDT (USEPA 1988): 5E-4 mg/kg/day.

Other Regulations and Standards to be Considered

WHO/FAO ADI (ATSDR 1988): 5 μg/kg/day for DDT.

OSHA Standard (air): TWA[1] = 1 mg/m^3

ACGIH Threshold Limit Value: TWA = 1 mg/m^3

FDA Action Levels: FDA has set action levels for residues of DDT and DDE in 52 food categories ranging from 0.05 ppm in fish and tomatoes to 1.25 ppm in milk.

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[1] 8 hour time weighted average.

D_T Value

The D_T value is defined as that contaminant intake rate (mg/kg/day) that should not induce an adverse effect to human health or should not pose a risk of cancer occurrence greater than a predetermined risk level.

For carcinogens such as DDT and its isomers, the D_T value is based on the USEPA Carcinogen Assessment Group's cancer potency slopes. The cancer potency slopes have been estimated for oral exposure routes and for inhalation exposure for some chemicals. The slopes are intended to be a plausible upper bound of the potency of a carcinogen in inducing cancer at low doses. Calculation of a D_T using a cancer potency slope requires selection of an acceptable cancer risk level. A range of risk levels from 10^{-4} to 10^{-6} is considered for all carcinogens, therefore a range of D_T values based on the respective U.S. EPA cancer potency factors for DDT, DDD and DDE is presented. Derivation of the oral and inhalation D_T values for DDT is as follows:

$$D_T = \frac{\text{Risk Level}}{\text{Potency Slope (mg/kg/day)}^{-1}}$$

$$= \frac{1 \times 10^{-4}}{0.34}$$

$$= 2.9 \times 10^{-4} \text{ mg/kg/day}$$

The ranges for DDT, DDD and DDE based on their respective U.S. EPA cancer potency factors are presented below:

DDT Contaminant Intake Rate Comparisons:

Risk Level	D_T Oral Exposure (mg/kg/day)	D_T Inhalation Exposure (mg/kg/day)
10^{-4}	2.9×10^{-4}	2.9×10^{-4}
10^{-5}	2.9×10^{-5}	2.9×10^{-5}
10^{-6}	2.9×10^{-6}	2.9×10^{-6}

DDD Contaminant Intake Rate Comparisons:

Risk	D_T Oral Exposure (mg/kg/day)
10^{-4}	4.2×10^{-4}
10^{-5}	4.2×10^{-5}
10^{-6}	4.2×10^{-6}

DDE Contaminant Intake Rate Comparisons:

Risk	D_T Oral Exposure (mg/kg/day)
10^{-4}	2.9×10^{-4}
10^{-5}	2.9×10^{-5}
10^{-6}	2.9×10^{-6}

Comparative D_T Values

The U.S. EPA (1988) cancer potency factor for DDT (0.34/mg/kg/day) was derived from six studies reporting tumors of the liver in rats and mice. This slope factor is the geometric mean of the individual slope factors derived from the DDT rat and mice studies. The U.S. EPA (1989a) cancer potency factor for DDD (0.24/mg/kg/day) was derived from a study of mouse liver tumors. The U.S. EPA (1989b) cancer potency factor for DDE is the geometric mean of six upper bound slope factors (q_1*s) derived from studies reporting liver tumors in mice and hamsters upon oral exposure.

These U.S. EPA cancer potency factors represent the 95% upper confidence limit computed using the linearized multi-stage model of carcinogenesis. A number of alternative slope factors for DDT, DDD, and DDE can be derived from individual animal studies, as a basis of comparison. From these alternative slope values, a series of alternative D_T values may be derived. Table 1 shows a number of alternative contaminant intake rates (D_T) at the 10^{-5} risk level.

TABLE 1

Alternative Contaminant Intake Values (D_T)

for DDT, DDD, and DDE at 10^{-5} Risk Level*

Study[1]	Compound	Species	Endpoint	D_T 95% UCL[2] (mg/kg/day)	D_T M.L.E.[3] (mg/kg/day)
Rossi et al. 1983	DDT	♀ hamsters	adrenal adenomas	2.0×10^{-4}	3.5×10^{-4}
Cabral et. al. 1982	DDT	♀ rats	liver tumors	1.2×10^{-4}	1.8×10^{-4}
Rossi et al. 1977	DDT	♂ rats	liver tumors	6.3×10^{-5}	1.1×10^{-4}
Rossi et al. 1977	DDT	♀ rats	liver tumors	3.7×10^{-5}	5.6×10^{-5}
Thorpe and Walker 1973	DDT	♂ mice	benign liver tumors	5.3×10^{-6}	8.3×10^{-6}
Thorpe and Walker 1973	DDT	♂ mice	malignant liver tumors	1.9×10^{-5}	3.1×10^{-5}

Thorpe and Walker 1973	DDT	♀ mice	benign liver tumors	3.7×10^{-6}	5.6×10^{-6}
Thorpe and Walker 1973	DDT	♀ mice	malignant liver tumors	1.2×10^{-5}	1.9×10^{-5}
Tarjan and Kemeny 1969	DDT	♂ and ♀ F_2 generation mice	lung carcinomas	5.8×10^{-7}	9.4×10^{-7}
Tarjan and Kemeny 1969	DDT	♂ and ♀ F_3 generation mice	lung carcinomas	1.0×10^{-6}	1.8×10^{-6}
Tarjan and Kemeny 1969	DDT	♂ and ♀ $_4$ generation mice	lung carcinomas	1.4×10^{-6}	1.8×10^{-6}
Tarjan and Kemeny 1969	DDT	♂ and ♀ F_5 generation mice	lung carcinomas	1.3×10^{-6}	1.6×10^{-6}
Tarjan and Kemeny 1969	DDT	♂ and ♀ F_2 generation mice	leukemia	2.0×10^{-6}	8.3×10^{-6}
Tarjan and Kemeny 1969	DDT	♂ and ♀ F_3 generation mice	leukemia	1.1×10^{-6}	1.8×10^{-6}

Tarjan and Kemeny 1969	DDT	♂ and ♀ F_4 generation mice	leukemia	1.6×10^{-6}	2.2×10^{-6}
Tarjan and Kemeny 1969	DDT	♂ and ♀ F_5 generation mice	leukemia	2.1×10^{-6}	3.0×10^{-4}
Terracini et al. 1973	DDT	♂ parental and F_1 generation mice	benign liver tumors	1.4×10^{-4}	1.0×10^{-1}
Terracini et al. 1973	DDT	♀ parental generation mice	benign liver tumors	3.8×10^{-5}	1.6×10^{-4}
Terracini et al. 1973	DDT	♀ F_1 generation mice	benign liver tumors	1.1×10^{-4}	4.7×10^{-2}
Turusov et al. 1973	DDT	♂ parental generation mice	benign liver tumors	1.7×10^{-5}	2.6×10^{-5}
Turusov et al. 1973	DDT	♂ F_1 generation mice	benign liver tumors	1.1×10^{-5}	1.6×10^{-5}
Turusov et al. 1973	DDT	♂ F_2 generation mice	benign liver tumors	1.1×10^{-5}	1.5×10^{-5}
Turusov et al. 1973	DDT	♂ F_3 generation mice	benign liver tumors	1.1×10^{-5}	1.6×10^{-5}

Turusov et al. 1973	DDT	♂ F_4 generation mice	benign liver tumors	9.1×10^{-6}	1.9×10^{-5}
Turusov et al. 1973	DDT	♂ F_5 generation mice	benign liver tumors	1.7×10^{-5}	4.2×10^{-5}
Turusov et al. 1973	DDT	♀ parental generation mice	benign liver tumors	2.7×10^{-5}	7.7×10^{-5}
Turusov et al. 1973	DDT	♀ F_1 generation mice	benign liver tumors	2.1×10^{-5}	4.5×10^{-5}
Turusov et al. 1973	DDT	♀ F_2 generation mice	benign liver tumors	2.7×10^{-5}	3.8×10^{-5}
Turusov et al. 1973	DDT	♀ F_3 generation mice	benign liver tumors	2.3×10^{-5}	6.3×10^{-5}
Turusov et al. 1973	DDT	♀ F_4 generation mice	benign liver tumors	1.9×10^{-5}	3.3×10^{-5}
Turusov et. al. 1973	DDT	♀ F_5 mice	benign liver tumors	2.7×10^{-5}	6.3×10^{-5}
Tomatis et al. 1974	DDE	♂ mice	benign liver tumors	1.8×10^{-5}	2.7×10^{-5}
Tomatis et al. 1974	DDE	♀ mice	benign liver tumors	3.9×10^{-6}	6.1×10^{-6}

Tomatis et al. 1974	DDD	♂ mice	benign liver tumors	4.0×10^{-5}	7.3×10^{-5}
Tomatis et al. 1974	DDD	♀ mice	benign liver tumors	4.5×10^{-4}	4.2×10^{-3}
NCI 1978	DDB	♂ mice	hepatocellular carcinomas	2.9×10^{-5}	9.1×10^{-5}
NCI 1978	DDB	♀ mice	hepatocellular carcinomas	1.2×10^{-5}	3.2×10^{-5}
Rossi et al. 1983	DDB	♂ hamsters	benign liver tumors	1.1×10^{-4}	1.6×10^{-4}
Rossi et al. 1983	DDB	♀ hamsters	benign liver tumors	2.2×10^{-4}	3.6×10^{-4}

* The multistage model was used to derive these values.

References

Agency for Toxic Substances and Disease Registry (ATSDR). 1988. Draft Toxicological Profile for DDT, DDE, and DDD. U.S. Public Health Service.

American Conference of Governmental Industrial Hygienists (ACGIH). 1980. Documentation of the threshold limit values. 4th ed. Cincinnati, Ohio.

ASTM. 1985. Standard practice for conducting bioconcentration tests with fishes and saltwater bivalve mollusca. Designation E 1022-84, pages 590-62. In: 1985 Annual Book of ASTM Standards Volume 11.04. American Society for Testing and Materials, Philadelphia, Pennsylvania.

Briggs, G.G. 1981. Theoretical and experimental relationships between soil adsorption, octanol-water partition coefficients, water solubilities, bioconcentration factors, and the parachor. J. Agric. Food Chem. 29:1050-1059.

Burrows, W.D., D.R. Cogley, W.G. Light, J.C. Dacre, and G. Woodard. 1979. Problem definition studies on potential environmental pollutants. VII. Physical, chemical, toxicological and biological properties of DDT and its derivatives. Technical Report 7906, U.S. Army Medical Bioengineering Research and Development Laboratory, Fort Detrick, Frederick, MD.

Casarett and Doull's Toxicology. 1980. The basic science of poisons. Second edition. Doull, J., Klaassen, C.D., and Amdur, M.O. (editors). Macmillan Publishing Company, Inc., New York.

Chiou, C.T., J.L. Peters and V.H. Freed. 1979. A physical concept of soil-water equilibria for nonionic organic compounds. Science, 206:831-832.

Davies, R.P. and A.J. Dobbs. 1984. The prediction of bioconcentration in fish. Water Res. 18(10): 1253-1262.

Executive Office of the President (EOP). 1971. Ecological effects of pesticides on non-target species. Office of Science and Technology, Washington, D.C. EOP/OST-71.

Hansch, C. and A.J. Leo. 1979. Substituent constants for correlation analysis in chemistry and biology. John Wiley and Sons, New York, NY.

International Agency for Research on Cancer (IARC). 1987. IARC monographs on the evaluation of carcinogenic risks in humans. Supplement 7.

Kadeg, R.D., S.I. Pavlou, and A.S. Duxbury. 1986. Elaboration of sediment normalization theory for non-polar hydrophobic organic chemicals. U.S. Environmental Protection Agency, Criteria and Standards Division, Washington, D.C.

Kenaga, E.E. 1980. Correlation of bioconcentration factors of chemicals in aquatic and terrestrial organisms with their physical and chemical properties. Environ. Sci. Technol., 14(5):553-556.

Kimerle, R.A., W.E. Gladhill, and G.J. Levinskas. 1978. Environmental safety assessment of new materials. Estimating the hazard of chemical substances to aquatic life, ASTM, STP 657, John Cairns, Jr., K.L. Dickson and A.W. Maki, eds., American Society for Testing and Materials, 1978. pp. 132-146.

Lyman, W.J. and C.P. Loreti. 1987. Prediction of soil and sediment sorption for organic compounds. Final report. U.S. Environmental Protection Agency,

Monitoring and Data Support Division, Office of Water Regulations and Standards. Washington, D.C.

Lyman, W.J., W.F. Reehl, and D.H. Rosenblatt. 1982. Handbook of chemical property estimation methods: Environmental behavior of organic compounds. McGraw-Hill Book Co., New York.

National Institute for Occupational Safety and Health (NIOSH). 1982. Registry for toxic effects of chemical substances. Volumes I-III. U.S. Department of Health and Human Services. Cincinnati, OH.

National Institute for Occupational Safety and Health (NIOSH). 1978. Special occupational hazard review for DDT. Rockville, Maryland. DHEW Publication No. (NIOSH) 78.200.

National Toxicology Program (NTP). 1986. Fiscal year 1986 annual plan. U.S. Department of Health and Human Services. Public Health Service. Washington, D.C. NTP-86-085. May 1986.

Pavlou S.P. 1980. Thermodynamic aspects of equilibrium sorption of persistent organic molecules at the sediment-seawater interface: A framework for predicting distributions in the aquatic environment. In: Contaminants and sediments. Volume 2. Baker, R.A. (editor). Science Publishers, Inc. Ann Arbor, MI.

Rao, P.S.C. and J.M. Davidson. 1983. Estimation of pesticide retention and transformation parameters required in nonpoint source pollution models. In Overcash, M.R. and J.M. Davidson, editors. Environmental Impact of Nonpoint source Pollution. Ann Arbor Science Publishers, Inc., Ann Arbor, MI.

Sabljic, A. 1984. Predictions of the nature and strength of soil sorption of organic pollutants by molecular topology. J. Agric. Food Chem. 32:243-346.

U.S. Environmental Protection Agency (USEPA). 1979. Water-related environmental Fate of 129 priority pollutants. Washington, D.C. December 1979. EPA 44/4-79-029.

U.S. Environmental Protection Agency (USEPA). 1980. Ambient water quality criteria for DDT. Office of Water Regulations and Standards, Criteria and Standards Division. Washington, D.C. October 1980. EPA 440/5-80-038.

U.S. Environmental Protection Agency (USEPA). 1984. Health effects assessments for DDT. Environmental Criteria and Assessment Office, Cincinnati, Ohio. September 1984. ECAO-CIN-H026 (Final Draft).

U.S. Environmental Protection Agency (USEPA). 1985. Health assessment document for dichloromethane (methylene chloride). Office of Health and Environmental Assessment. Washington, D.C. February 1985. EPA 600/8-82/004F.

U.S. Environmental Protection Agency (USEPA). 1986a. Superfund public health evaluation manual. Office Emergency and Remedial Response. Washington, D.C. EPA 540/1-86/060.

U.S. Environmental Protection Agency (USEPA). 1986b. Quality criteria for water, 1986 ("The Gold Book"). Office of Water Regulations and Standards, Washington, D.C. EPA 440/5-86-001.

U.S. Environmental Protection Agency (USEPA). 1986c. The assessment of the carcinogenicity of dicofol (kelthane), DDT, DDE, and DDD (TDE). Office of Health and Environmental Assessment. EPA/600/6-86/001.

U.S. Environmental Protection Agency (USEPA). 1988. Integrated Risk Information System (IRIS). Access Date: January 8, 1990. [Note: This is a computerized data base.]

U.S. Environmental Protection Agency (USEPA). 1989a. Integrated Risk Information System (IRIS). Access Date: January 8, 1990. [Note: This is a computerized data base.]

U.S. Environmental Protection Agency (USEPA). 1989b. Integrated Risk Information System (IRIS). Access Date: January 8, 1990. [Note: This is a computerized data base.]

U.S. Food and Drug Administration (USFDA). 1987. Action levels for poisonous or deleterious substances in human food. Washington, D.C. March 1987.

Verschueren, K. 1977. Handbook of environmental data on organic chemicals. Van Nostrand Reinhold Co., New York. 659 pages.

Voerman, S. and A.F.H. Besemer. 1975. Persistence of Dieldrin, Lindane, and DDT in a light sandy soil and their uptake by grass. Bull. Environ. Contam. Toxicol. 13(4): 501-505.

Weast, R.E., ed. 1981. Handbook of chemistry and physics. 62nd ed. CRC Press, Cleveland, Ohio.

DIBROMOCHLOROPROPANE[1]

Summary

Dibromochloropropane (DBCP) is a persistent and environmentally mobile pesticide. Formerly, DBCP was used as a soil fumigant and nematocide. It is carcinogenic in mice and rats and mutagenic in bacterial systems and mammalian cell cultures. It causes forestomach, kidney, liver and mammary tumors (female rats) when administered orally. When administered via inhalation, it causes nasal, tongue, and lung tumors. Some men occupationally exposed to DBCP exhibit abnormally low sperm counts. Animal studies have shown that dibromochloropropane is cytotoxic and has adverse effects on the tests, liver, kidneys, respiratory tract, central nervous system, and blood cells.

CAS Number: 96-12-8
Chemical Formula: CH_5Br_2Cl
IUPAC Name: 1,2-Dibromo-3-chloropropane
Important Synonyms and Trade Names; DBCP, Fumazone, Nemagon

Chemical and Physical Properties

Molecular Weight:	236.36
Boiling Point:	196°C (Berkowitz et al. 1978)
Melting Point:	6°C
	5°C (Berkowitz et al. 1978)
Specific Gravity:	2.093 at 14°C
Solubility in Water:	1230 mg/liter (USEPA 1985a)
Solubility in Organics:	Miscible with oils, dichloropropane, and isopropyl alcohol.

Log Octanol/Water Partition Coefficient (Kow): 2.29 (Lyman et al. 1982)
Fragment Method

2.43 (USEPA 1985a)

Soil/Water Partition Coefficient (Koc):

130	Sabljic (1984) Table I (experimental)
175	Lyman and Loreti (1987) (log Kow = 2.29)
225	Lyman and Loreti (1987) (log Kow = 2.43)

Bioconcentration Factor:

41.4	Lyman et al. (1982) Eqn 5-2 (log Kow = 2.43)
67.5	Lyman et al. (1982) Eqn 5-2 (log Kow = 2.71)
11.2	Davies and Dobbs (1984) Eqn A (5 = 1,230)
63	Davies and Dobbs (1984) Eqn B (log Kow = 2.71)
43.5	Davies and Dobbs (1984) Eqn B (log Kow = 2.43)
35.9	Davies and Dobbs (1984) Eqn B (log Kow = 2.29)
19.8	Davies and Dobbs (1984) Eqn C (log Kow = 29)
27.6	Davies and Dobbs (1984) Eqn C (log Kow = 2.43)
32.4	Lyman et al. (1982) Eqn 5-2 (log Kow = 2.29)

Vapor Pressure: 0.8 mm Hg at 21°C (USEPA 1985a)
1.1 mm Hg at 25°C (estimated; Lyman et al. 1982)

Henry's Law Constant: 3.5×10^{-4} atm-m^3/mole at 20°C (Burlinson et al. 1982)
1.47×10^{-2} Dimensionless
3.11×10^{-4} atm-m^3/mole (USEPA 1985b)
1.31×10^{-2} Dimensionless

Transport and Fate

Dibromochloropropane (DBCP) is a persistent pesticides. The major route of its removal from soil and aqueous systems is by volatilization. DBCP is decomposed slowly in soil both by microbial action and by hydrolysis (USEPA 1985b). DBCP may be converted to n-propanol, bromide, and chloride by soil-water culture (Berkowitz et al. 1978). A range of estimated and experimental soil-water partition coefficients is reported above and indicates that sorption of DBCP to soils sediments and dissolved organic material will occur. The combined water solubility and organic partitioning data for dibromochloropropane suggest that this compound will exhibit some degree of environmental mobility.

Plant uptake can occur with DBCP levels generally highest in the root portion. Bromide ion has also been shown to be present in increased levels in plants grown in DBCP-treated fields (Guinn and Potter 1962), and may be due to microbial or plant enzyme activity.

A range of estimated bioconcentration factors (BCFs) for DBCP is also reported above. ASTM (1985) indicates that chemicals with bioconcentration factors less than approximately 100 have low potential for causing harm to wildlife and human health via biomagnification of residues up food chains. The magnitude of the concentration factors suggests that appreciable bioconcentration or biomagnification of DBCP residues is not likely to occur.

Health Effects

1. DBCP produces tumors in rats and mice of both sexes when administered by inhalation, dietary feeding or gastric gavage.

2. In each oral and inhalation study a tumor response occurred at the site of first contact (stomach - oral; nasal cavity, lung - inhalation) and in some cases at other sites as well.

3. The stomach tumors occur in the non-glandular stomach, a structure that is not present in man. Tumors did not occur in the glandular stomach, the region of the rat stomach more closely related to the human stomach.

4. Acute high doses of DBCP, greater than 20 mg/kg, produces tissue damage and necrosis of the nasal cavity, kidney tubule, liver cells and testes. Chronic oral exposure at 2.39 mg/kg for 1 year causes necrosis of kidney cells in female rats.

5. DBCP, has been classified according to EPA's Proposed Guidelines for Carcinogenic Risk Assessment in EPA's Group B2 (inadequate evidence in humans) based on positive results in animal studies and inadequate data in humans (50 Federal Register 46989, Wed. Nov. 13, 1985).

In studies with DBCP, the National Toxicology Program (NTP) reported no effects on dominant lethal frequency in mice receiving intraperitoneal and subcutaneous injections (NTP 1985). It has also caused somatic cell mutations and chromosomal aberrations in Drosophila melanogaster (USEPA 1985b). Chromosome aberrations and positive evidence of sister chromatic exchange have been reported in Chinese hamster ovary cells (NTP 1986).

Some men occupationally exposed to DBCP during its manufacture were found to have abnormally low sperm counts (USEPA 1985b). The available data does not allow for quantitative dose-response evaluation from the epidemiology data. However, the animal studies are illuminating on this point. Male rats and rabbits exposed to DBCP during subchronic inhalation toxicity studies were found to have

abnormally low sperm cells as well as degenerative changes in the seminiferous tubules, decreased weight of the testes, and an increased proportion of abnormal sperm cells (USEPA 1985b) after 14 weeks exposure to 10 ppm (19.6 mg/kg) in rats or 1.0 ppm (1.44 mg/kg) in rabbits. The no-effect levels were 1 ppm (1.96 mg/kg) in rats and 0.1 ppm (0.144 mg/kg) in rabbits. More recent studies using drinking water routes of exposure have demonstrated no-effect levels of 37.6 ppm (0.94 mg/kg) in rabbits. In rats water levels of 200 ppm DBCP did not affect fertility, sperm counts, male reproductive hormone levels or microscopic structure of the testis. Sperm counts were decreased in rats when a dose of 15 mg/kg in corn oil was administered by gavage. (Shell, 1986). The animal studies have clearly demonstrated that the effect of DBCP on male reproduction follows dose-response principles and definitive no-effect levels have been shown.

Liver and kidney effects have also been noted in animal studies. Effects range from dilatation of the sinusoids and centrilobular congestion to cirrhosis and necrosis in the liver. Cloudy swelling of the epithelium of the proximal convoluted tubules and increased amounts of interstitial tissue have been found in the kidneys (USEPA 1985b). Effects on blood cells were also noted in several studies. These effects include severe leukopenias and anemias in exposed monkeys and decreased activity of phagocytic cells in exposed rats (USEPA 1985b). At toxic doses there is cellular damage that in the extreme leads to necrosis (death of cells). Tissue damage, cytotoxicity, has been observed in all target organs that later develop tumors. (Shell, 1986) The cytotoxicity leading to cell death and cell replacement may be responsible in part for the increased incidence of tumors. The tumors occurred at sites where cells have the natural ability to replicate.

Toxicity to Wildlife and Domestic Animals

The acute oral LD50 value of DBCP to female mallard ducks is 66.8 mg/kg and 156 mg/kg in female pheasants. Both avian LD50 values are lower than the acute oral

LD50 value of the rat (400 mg/kg) and indicate an increased sensitivity of these animals. Exposure to a water concentration of 1 mg/liter DBCP for 24 hours produced a 90 percent mortality in clam larvae. At a use concentration of 20 gallons DBCP per acre, 100 percent of exposed earthworms died in 1 day. At a use rats of 5 pounds per acre, DBCP killed 87 percent of the Lumbricus and 28 percent of the Helodrilus sp. in 32 days.

Regulations and Standards

NIOSH Recommended Standard: 10 ppb (0.1 mg/m^3)

National Primary Drinking Water Standard (USEPA): Zero

(Proposed RMCL; 50 Federal Register 46988, Wednesday, November 13, 1985)

OSHA Standard (air): TWA (time weighted average) 1 ppb (9.6 ug/m^3)

EPA has produced several risk estimates for DBCP. The June 8, 1978 value was based on a multihit model applied to the NCI gavage dosing studies and yielded the equation:

$P(x) = 1.209 \times 10^{-5} d$, where d was ng/kg/day.

This is equivalent to:

$P(x) = 12.9 \times d$, where d is mg/kg/day, the same dose scale as presently used in tables of potency.

CAG Upper Bound Potency Slope for Oral Exposure (USEPA 1985c): 1.4 $(mg/kg/day)^{-1}$.

Shell (1986) conducted an extensive risk assessment on DBCP several models and dose scaling factors. The tumor incidence data were obtained from the 2 year rat feeding study. The tumor incidence in the male rats gave the highest estimates of cancer risk as follows:

Model	Potency for Lifetime risk, mg/kg dose scale Maximum likelihood estimates	
Weibull	3.85×10^{-3}	$(mg/kg/day)^{-1}$
Multihit	3.5×10^{-4}	$(mg/kg/day)^{-1}$
Multistage	1.4×10^{-1}	$(mg/kg/day)^{-1}$

The geometric mean of the above 3 models is 6.04×10^{-3} $(mg/kg/day)^{-1}$ which is one indicator of central tendency. Including the logit and probit models with the previous 3 models (see risk assessment for details) provides another measure of central tendency across 5 models and yields a potency was 9.1×10^{-3} $(mg/kg/day)^{-1}$ which is not much different than the geometric mean of the 3 models.

The risk was also estimated using the female tumor incidence. Only the multistage model predicted mush risk and the potency was 7×10^{-4} $(mg/kg/day1)^{-1}$.

D_T Value

The D_T value is defined as that contaminant intake rats (mg/kg/day) that should not induce an adverse effect to human health or should not pose a risk of cancer occurrence greater than a predetermined risk level.

The first D_T value is based on the USEPA Cancer Assessment Group's cancer potency slopes. The cancer potency slope was estimated for oral exposure routes using the linearized multistage model and the rat feeding study data. The slopes are intended to be a plausible upper bound of the potency of a carcinogen in inducing cancer at low doses. Calculation of a D_T using a cancer potency slope requires selection of an acceptable cancer risk level. A range of risk levels from 10^{-4} to 10^{-6} is considered for all carcinogens, therefore a range of D_T values is presented. Derivation of the D_T values is as follows:

$$D_T = \frac{\text{Risk Level}}{\text{Potency Slope (mg/kg/day)}^{-1}}$$

$$= \frac{1 \times 10^{-4}}{1.4 \text{ (mg/kg/day)}^{-1}}$$

$$= 1.1 \times 10^{-5} \text{ (mg/kg/day)}$$

The range of D_T values from DBCP is presented below:

Risk Level	D_T (mg/kg/day)
10^{-4}	7.1×10^{-5}
10^{-5}	7.1×10^{-6}
10^{-6}	7.1×10^{-7}

A range of D_Ts based on alternative and equally plausible dose-response models have been calculated based on the Weibull, Multihit, Multistage, and geometric mean as follows:

Model	D_T (mg/kg/day) at several risk levels		
Male data	10^{-4}	10^{-5}	10^{-6}
Weibull	2.6×10^{-2}	1.6×10^{-3}	2.6×10^{-4}
Multihit	2.9×10^{-1}	2.9×10^{-2}	2.9×10^{-3}
Multistage	7.1×10^{-4}	7.1×10^{-3}	7.1×10^{-6}
Geometric mean of above	1.7×10^{-2}	1.7×10^{-3}	1.7×10^{-4}
Female data			
Multistage	1.1×10^{-2}	1.1×10^{-3}	1.1×10^{-4}

The D_T for reproductive effects have been calculated. Using the rabbit inhalation no-effect level (0.144 mg/kg) yields an inhalation D_T of 0.000144 mg/kg with a 100 fold safety factor, using the most sensitive species. The corresponding value with 100 fold safety factor using the rat data is 0.019 mg/kg. Using the oral route of exposure data the no-effect level for the rabbit was 1 mg/kg or with a 100 fold safety factor a D_T = 0.01 mg/kg.

CERTAINTY AND UNCERTAINTY IN THE D_{τ} AND SUPPORTING TOXICOLOGY

DBCP is a reproductive toxin in male animals and human males when the exposure is sufficient. No-effect levels have been established in animal studies using gavage and drinking water routes of exposure. There is a high degree of certainty that a D_{τ} of 0.01 mg/kg/day would be protective for reproductive effects.

DBCP is cytotoxic resulting in cell injury and death. Levels of 1 ppm in air can result in epithelial cell damage in the nasal passages. Cytotoxicity has been observed in all tissues and organs where tumors have occurred in lifetime exposure studies.

DBCP is an animal carcinogen in rats and mice. In the rat study there was a sex difference with more tumors at lower doses in the males than in the females.

Using different dose-response models yields a range of D_{τ} values with a range of uncertainty of about 3 orders of magnitude or more. It is plausible but not proven that DBCP at low rates of exposure either presents no cancer risk to humans or a risk much lower than that extrapolated from high doses. Using the 10^{-4} risk level as a discussion point the EPA upper bound on the risk gives a D_{τ} of 7.1×10^{-5} mg/kg/day. The maximum likelihood estimate from the multistage model yields a D_{τ} of 7.1×10^{-4} or one order of magnitude larger. The other models yield D_{τ}s of 2.6×10^{-2} (Weibull) and 2.9×10^{-1} (Multihit) which are 300 to 4000 times larger than the D_{τ} based on the upper bound of risk. The geometric mean of the 3 maximum likelihood estimates yields a D_{τ} of 1.7×10^{-2} which is 200 times larger than the D_{τ} based on the upper bound of risk. The D_{τ} based on a 100 fold safety factor and a no-effect level for reproductive effects, which includes protecting against cytotoxicity, is 1×10^{-2} which is 200 times larger than the D_{τ} based on the upper bound of risk. The geometric mean of the 3 maximum likelihood estimates yields a D_{τ} of 1.7×10^{-2} which is 200 times larger than the D_{τ} based on the upper bound of risk. The D_{τ}

based on a 100 fold safety factor and a no-effect level for reproductive effects, which includes protecting against cytotoxicity, is 1×10^{-2} mg/kg/day. On this basis the Weibull and Multihit D_{τ}s at 10^{-4} risk while estimating protective doses for cancer would not provide a conventional safety margin for reproductive effects. At a D_{τ} of 1×10^{-2} mg/kg/day the calculated cancer risks range from the upper bound value of 1.4×10^{-2} down to 3.5×10^{-6} for the multihit model.

If DBCP acts at least in part through a non-genotoxic, cytotoxicity, increased rates of cell replication cancer mechanism than the D_{τ} that protects against reproductive effects and cytotoxicity would have the effect of reducing the low dose cancer risk. This is a plausible, but not proven alternative.

REFERENCES

ASTM. 1985. Standard Practice for Conducting Bioconcentration Tests with Fishes and Saltwater Bivalve Mollusca. Designation E 1022-84, pages 590-62. In: 1985 Annual Book of ASTM Standards Volume 11.04. American Society for Testing and Materials, Philadelphia, Pennsylvania.

BERKOWITZ, J.B., M.M. GOYER, J.C. HARRIS, H.J. LYMAN, R.A. HORNE, L.H. NELKEN, J.E. HARRISON, and D.H. ROSENBLATT. 1978. Literature Review--Problem Definition Studies on Selected Chemicals. Final Report. Vol. II. Chemistry, Toxicology, and Potential Environmental Effects of Selected Organic Pollutants. Contract No. DAMD 17-77-C-7037, Arthur D. Little, Inc. Cambridge, MA (AD B052946L).

MERCK INDEX. 9th ed. Windholz, M., Ed. Merck and Co., Rathway, New Jersey.

NATIONAL CANCER INSTITUTE (NCI). 1977. Bioassay of Dibromochloropropane for Possible Carcinogenicity. CAS No. 96-12-8. NCI Carcinogenesis Technical Report Series No. 28, Washington, D.C. DHEH Publication No. (NIM) 78-828.

NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH (NIOSH). 1978. A Recommended Standard for Occupational Exposure to Dibromochloropropane. Center for Disease Control, NIOSH, Cincinnati, Ohio. DHEH Publication No. (NIOSH) 78-115.

NATIONAL TOXICOLOGY PROGRAM (NTP). 1985. Fiscal Year 1985 Annual Plan. U.S. Department of Health and human Services. Public Health Service. Washington, D.C. NTP-85-055. March 1985.

NATIONAL TOXICOLOGY PROGRAM (NTP). 1986. Fiscal Year 1986 Annual Plan. U.S. Department of Health and Human Services. Public Health Service. Washington, D.C. NTP-86-086. May 1986.

PAVLOU, S.P. 1980. Thermodynamic Aspects of Equilibrium Sorption of Persistent Organic Molecules at the Sediment-Seawater Interface: A Framework For Predicting distributions in the Aquatic Environment. IN: Contaminants and Sediments. Volume 2. Baker, R.A. (Editor). Science Publishers, Inc. Ann Arbor, MI.

SHELL, (1986) Risk Assessment of DBCP

SABINIC, A. 1984. Predictions of the nature and strength of soil sorption of organic pollutants by molecular topology. J. Agric. Food chem. 32:243-246.

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). 1979. Water-Related environmental Fate of 129 Priority Pollutants. Washington D.C. December 1979. EPA 440/4-79-029.

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). 1985a. Draft Health Advisory for 1,2-dibromo-3-chloropropane (DBCP). Office of Drinking Water. U.S. Environmental Protection Agency. Washington, DC.

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). 1985b. Drinking Water Criteria Document for 1,2-dibromo-3-chloropropane (DBCP). Environmental Criteria and Assessment Office. cincinnati, OH. EPA-600/X-84-209. PB86-1180894/HEB.

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). 1986. Superfund Public Health Evaluation Manual. Office of Emergency and Remedial Response, Washington, D.C. EPA 540/1-86/060.

1,1-DICHLOROETHANE

Summary

1,1-Dichloroethane was at one time used as an anesthetic, but is no longer used for this purpose because of its marked excitation of the heart. It is not manufactured in the U.S. but is imported for limited use as a solvent, chemical intermediate and cleaning agent (U.S. EPA 1980a). 1,1-Dichloroethane is volatile and therefore not likely to be persistent in aquatic environments. It is a flammable, colorless, oily liquid only slightly soluble in water. NIOSH has estimated the number of workers exposed at 4,600 (Sittig 1985). Inhalation exposure to high doses causes central nervous system depression and cardiac arrhythmia in humans and may cause hepatotoxicity and kidney injury. In animals, high doses cause liver and kidney damage and retarded fetal development. Negative results were obtained in the Ames assay for mutagenicity.

CAS Number:	75-34-3
Chemical Formula:	CH_3CHCl_2
IUPAC Name:	1,1-Dichloroethane
Important Synonyms and Trade Names:	Ethylidene chloride; Ethylidene dichloride, asymmetrical dichloroethane (Sittig 1985)

Chemical and Physical Properties

Molecular Weight:	98.96
Boiling Point:	57.3°C
Melting Point:	-97°C
Specific Gravity:	1.1776 at 20°C
Solubility in Water:	5.5 g/liter (USEPA 1986a) 8.1 g/liter (ECAO 1980) 8.45 g/liter (Chiou 1976) 0.5 g/100 ml at 20°C (Torkelson and Rowe 1981)
Solubility in	

Organics:		Miscible in alcohol
Log Octanol/Water Partition Coefficient (K_{ow}):		1.8 (USEPA 1986a) 1.92 (Lyman et al. 1982)
Soil-Water Partition Coefficient (K_{oc}):		
	227	Lyman et al. (1982) Eqn 4-8 (log K_{ow} = 1.8)
	73	Lyman and Loreti (1987) (log K_{ow} = 1.8)
	30	USEPA (1986a)
Bioconcentration Factor (BCF):		
	16.95	Lyman et al. (1982) Eqn 5-2 (log K_{ow} = 1.92)
	5.1	Davies and Dobbs (1984) Eqn A (S = 5,000)
	2.3	Davies and Dobbs (1984) Eqn B (log K_{ow} = 1.9)
	11	Davies and Dobbs (1984) Eqn C (log K_{ow} = 1.8)
	18	Davies and Dobbs (1984) Eqn B (log K_{ow} = 1.8)
	14	Lyman et al. (1982) Eqn 5-2 (log K_{ow} = 1.8)
Vapor Pressure:		180 mm Hg at 20°C (Valvani et al. 1980) 182 mm Hg at 20°C (USEPA 1986a) 234 torr at 25°C (Torkelson and Rowe 1981)
Henry's Law Constant:		6×10^{-4} atm-m^3/mole (calculated) 4.31×10^{-3} atm-m^3/mole (USEPA 1986a) 1.81×10^{-1} Dimensionless

Transport and Fate

1,1-Dichloroethane disperses from surface water primarily by volatilization into the troposphere, where it is subsequently broken down by hydroxylation. The half-life of 1,1-dichloroethane in air is 1.5 months and in water the half-life is estimated to be 1-5 days (USEPA 1984).

A range of estimated soil-water partition coefficients (K_{oc}) is reported above and indicates that some sorption of 1,1-dichloroethane to soils/sediments and dissolved organic material will occur. Pavlou (1980) estimates that sorption of volatile organic compounds will range from low to moderate. The combined water solubility and

organic partitioning of 1,1-dichloroethane suggest that this compound will exhibit some degree of environmental mobility. One study has shown that aeration of solvent-contaminated groundwater reduced the level of 1,1-dichloroethane from 6 mg/l to 1 mg/l, an 83% removal rate (Love and Eilers 1982).

A range of estimated bioconcentration factors (BCFs) for 1,1-dichloroethane is also presented above. ASTM (1985) indicates that chemicals with bioconcentration factors less than approximately 100 have low potential for causing harm to wildlife and human health via biomagnification of residues up food chains. The magnitude of the concentration factors suggests that appreciable bioconcentration or biomagnification of 1,1-dichloroethane residues is not likely to occur.

Health Effects

Limited toxicological testing of 1,1-dichloroethane has been undertaken. The literature indicates that 1,1-dichloroethane is one of the least toxic of the chlorinated ethanes. The oral LD_{50} value in the rat is 725 mg/kg (NIOSH 1989). Little information about the toxicokinetics or metabolism of 1,1-dichloroethane is currently available, other than the fact that it is excreted in the expired air of dogs following inhalation exposure (Dow Chemical Co. unpublished as reported in Torkelson and Rowe 1981). There was no evidence of absorption through the skin of rabbits after repeated applications; when evaporation was restricted only a typical defatting action occurred (Dow Chemical Co. unpublished as reported in Torkelson and Rowe 1981).

No evidence of tissue alterations or disease were observed in a subchronic inhalation study whereby rats were exposed 7 hours/day, 5 days/week for 6 months to 500 or 1000 ppm 1,1-dichloroethane (Dow Chemical Co. unpublished as reported in ACGIH 1980). Guinea pigs, rabbits, and dogs also examined did not exhibit adverse effects. In an acute inhalation study, rats exposed to 4,000-17,500 ppm experienced liver injury (Sax 1975 as reported in U.S. EPA 1980b). In mice, acute intra-peritoneal administration of 1000 mg/kg was reported to have caused renal tubular swelling; high doses (2000 and 4000 mg/kg) caused increased urinary protein and urinary glucose, respectively, which is indicative of renal dysfunction (Plaa and

Larson 1965 as reported in Torkelson and Rowe 1981). Rats exposed for 8 hours to 4,000 ppm 1,1-dichloroethane in air survived but those exposed at the 16,000 ppm level for 8 hours did not (Smyth 1956 as reported in ACGIH 1980).

With regard to teratologic effects, rat fetuses exhibited delayed bone formation when pregnant rats were exposed on days 6-15 gestation to 3,800-6,000 ppm 1,1-dichloroethane vapors for 7 hours/day (Schwetz et al. 1974 as reported in Torkelson and Rowe 1981). No teratological effects were related to exposures. Dams exhibited slight but statistically significant decreases in food consumption and weight gain. Inhalation exposure to high doses of 1,1-dichloroethane (over 16,000 mg/m^3) caused retarded fetal development in rats (Schwetz et al. 1974).

A subchronic inhalation study of cats exposed 6 hours/day for 5 days/week for 13 weeks to 500 ppm 1,1-dichloroethane and subsequently exposed for another 13 weeks to 1000 ppm, revealed that kidney damage occurred only after the 1000 ppm dosing regime (Hofmann et al. 1971 as reported in Torkelson and Rowe 1981). Both histologic and biochemical (increased blood urea) evidence supported the adverse kidney effects results. The authors estimated a time-weighted average (TWA) dose of 750 ppm or 124.9 mg/kg/day; a low-adverse-effect-level (LOAEL) of 750 ppm can be assigned to this study. Exposure to the same levels was not associated with any adverse effects in rats, guinea pigs, or rabbits.

Human inhalation of 1,1-dichloroethane has been associated with liver, kidney, and hematopoiesis injury and lung irritation (Parker et al. 1979 as reported in U.S. EPA 1980b), as well as depression of the central nervous system (NIOSH 1978 as reported in U.S. EPA 1980a).

A carcinogenicity study that was conducted on rats did not establish any conclusive evidence suggesting that 1,1-dichloroethane causes cancer in laboratory animals (NCI 1978 as reported in U.S. EPA 1980b, Torkelson and Rowe 1981). Male Osborne-Mendel rats were fed 764 mg/kg/day by gavage for 78 weeks; $B6C3F_1$ male mice were fed 2885 or 1442 mg/kg/day and females were fed 3331 or 1664 mg/kg/day by gavage for 13 weeks. The slight increase in mammary cancer and hemangiosarcoma observed in female rats and the statistically significant increase in

uterine polyps that occurred in female mice were considered to be inconclusive evidence due to the large number of early deaths attributed to pneumonia and the very large doses used (NCI 1978 as reported in U.S. EPA 1980b).

Another carcinogenicity study examined the effects of continuous treatment with 835 mg/l or 2500 mg/l 1,1-dichloroethane administered in drinking water for 52 weeks to male $B6C3F_1$ mice using a two-stage treatment protocol (Klaunig et al. 1986). A total of 70 mice constituted the treatment group, 35 initiated by treatment with diethylnitrosamine (DENA) for 4 weeks while the remaining 35 received deionized drinking water. The positive control group received phenobarbital (PB) (500 mg/l) to examine differences in liver tumor promotion. Exposure to 1,1-dichloroethane did not affect the incidence or number of liver or lung tumors in either treatment group; the compound did not exhibit initiation or promotion responses with regard to carcinogenicity.

No mutagenic effects were observed in an in vitro bacterial assay using Salmonella typhimurium (Simon et al. 1977 as reported in U.S. EPA 1980a).

Toxicity to Wildlife and Domestic Animals

No information on the toxicity of 1,1-dichloroethane to aquatic species was reported in the literature reviewed. However, the available information on chloroethanes indicates that toxicity declines with decreases in chlorination (USEPA 1980). Therefore, the toxicity of 1,1-dichloroethane is probably similar to that of 1,2-dichloroethane, which is acutely toxic at levels ranging from 100-500 mg/liter (USEPA 1980). Chronic toxicity occurs at levels as low as 20 mg/liter (USEPA 1980).

No information on the toxicity of 1,1-dichloroethane to terrestrial wildlife or domestic animals was found in the sources reviewed.

Regulations and Standards

Ambient Water Quality Criteria (USEPA 1986b).

The available data are inadequate for establishing criteria.

OSHA Standard (air): TWA[1] = 400 mg/mg^3

ACGIH Threshold Limit Value:
TWA = 810 mg/m^3
TLV = 100 mg/m^3
STEL[2] = 1,010 mg/m^3

D_T Value

The D_T value is defined as that contaminant intake rate (mg/kg/day) that should not induce an adverse effect to human health or should not pose a risk of cancer occurrence greater than a predetermined risk level.

The oral D_T value of 1,1-dichloroethane is based on the same data used by EPA to derive the Reference Dose (RfD) specified in the Health Effects Assessment Summary Table (USEPA 1989). The supporting data are from a subchronic study (Hofmann et al. 1971) in which rats, cats, rabbits, and guinea pigs were exposed via inhalation to 2,025 mg/m^3 (500 ppm), 1,1-dichloroethane 6 hours/day, 5 days/week. No effects were reported in any of the animals tested. The EPA (USEPA 1984; 1989) used this data to estimate the No-Observed-Adverse-Effect-Level (NOAEL) in mg/kg/day as follows:

$$\text{NOEL} = \frac{(2025 \text{ mg/m}^3)(0.22 \text{ m}^3/\text{day})(0.5)(6 \text{ hr}/24 \text{ hr})(5 \text{ days}/7 \text{ days})}{0.35 \text{ kg}}$$

$$= 115 \text{ mg/kg/day}$$

The value of 0.22 m^3/day represents the default 24-hour rat breathing volume, 0.5 represents the assumed absorption coefficient, and 0.35 kg the default rat body weight.

An Uncertainty Factor (UF) of 1,000 is employed to address the extrapolation of results to humans (10), intraspecies variability (sensitive subgroups) (10), and the

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1 Time Weighted Average.

2 Short-Term Effect Level.

use of a subchronic rather than a chronic (lifetime) experimental study (10). Derivation of this D_T for 1,1-dichloroethane is as follows:

$$D_T = \frac{\text{NOEL (mg/kg/day)}}{\text{UF}}$$

$$= \frac{115}{1{,}000}$$

$$= 0.115 \text{ mg/kg/day [Note: EPA rounds this number 0.1 in their derivations.]}$$

The inhalation D_T value is also based on an RfD reported in USEPA 1989. The RfD is based on a subchronic study in which cats were exposed to 1,1-dichloroethane via inhalation 6 hours/day, 5 days/week for 13 weeks (Hofmann et al. 1981). The endpoint of concern was kidney damage (USEPA 1989). Additional study details were not available. An uncertainty factor of 1,000 was used in the derivation of RfD by EPA, yielding a value of 1.4×10^{-1} mg/kg/day. Additional details on the underlying study was not available.

REFERENCES

ASTM. 1985. Standard practice for conducting bioconcentration tests with fishes and saltwater bivalve mollusca. Designation E 1022-84, pages 590-62. In 1985 Annual Book of ASTM Standards Volume 11.04. Philadelphia: American Society for Testing and Materials.

American Conference of Governmental Industrial Hygienists (ACGIH). 1980. Documentation of the threshold limit values. Fourth edition. Cincinnati, OH: ACGIH.

Chiou, C.T., J.L. Peters and V.H. Freed. 1979. A physical concept of soil-water equilibria for nonionic organic compounds. Science 206:831-832.

Davies, R.P. and A.J. Dobbs. 1984. The prediction of bioconcentration in fish. Water Res. 18(10):1253-1262.

Elskamp, D.M.W. 1981. Toxicology of 1,1-dichloroethane. Report from the Medical Biological Laboratory, MBL-1981-14. Order No. PB82-182809. Washington, D.C.: NTIS.

Hofmann, H.T., H. Birnstiel, and P. Jobst. 1971. The inhalation toxicity of 1,1- and 1,2-dichloroethane. Arch. Toxikol. 27:248-265. (German, English abstract).

Kadeg, R.D., S.P. Pavlou, and A.S. Duxbury. 1986. Elaboration of sediment normalization theory for non polar hydrophobic organic chemicals. Washington, D.C.: U.S. Environmental Protection Agency, Criteria and Standards Division.

Klaunig, J.E., R.J. Ruch, and M. A. Pereira. 1986. Carcinogenicity of chlorinated methane and ethane compounds administered in drinking water to mice. Environ. Health Perspect. 69:89-95.

Love, O.T. and R.G. Eilers. 1982. Treatment of drinking water containing trichloroethylene and related industrial solvents. J. Am. Water Works Ass. August: 413-425.

Lyman W.J. and C.P. Loreti. 1987. Prediction of soil and sediment sorption for organic compounds. Final Report. Washington, D.C.: U.S. Environmental Protection Agency, Monitoring and Data Support Division, Office of Water Regulations and Standards.

National Cancer Institute (NCI). 1977. Bioassay of 1,1-dichloroethane for possible carcinogenicity. CAS No. 75-34-3. NCI Carcinogenesis Technical Report Series No. 66. DHEW Publication No. (NIH) 78-1316. Washington, D.C.: NCI.

National Institute for Occupational Safety and Health (NIOSH). 1983. Registry of toxic effects of chemical substances. Data Base. Washington, D.C.: NIOSH. October.

National Institute for Occupational Safety and Health (NIOSH). 1989. Registry of toxic effects of chemical substances. Cincinnati: NIOSH. December.

Pavlou, S.P. 1980. Thermodynamic aspects of equilibrium sorption of persistent organic molecules at the sediment-seawater interface: A framework for predicting distributions in the aquatic environment. In Contaminants and Sediments. Volume 2. R.A. Baker, (Ed.). Ann Arbor, MI: Science Publishers, Inc.

Schwetz, B.A., B.K.J. Leong, and P.J. Gehring. 1974. Embryo and fetotoxicity of inhaled carbon tetrachloride, 1,1-dichloroethane and methyl ethyl ketone in rats. Toxicol. Appl. Pharmacol. 28:452-464.

Sittig, M. 1985. Handbook of toxic and hazardous chemicals and carcinogens. Second edition. Park Ridge, NJ: Noyes Publications.

Torkelson, T.K. and V.K. Rowe. 1981. Halogenated aliphatic hydrocarbons. In Patty's industrial hygiene and toxicology, vol. 2B. Third edition, eds., G.D. Clayton and F.E. Clayton, 3175-3220. New York: John Wiley and Sons.

U.S. Environmental Protection Agency (USEPA). 1979. Water-related environmental fate of 129 priority pollutants. EPA 440/4-79-029. Washington, D.C.: USEPA. December.

U.S. Environmental Protection Agency (USEPA). 1980a. Ambient water quality criteria for chlorinated ethanes. EPA 440/5-80-028. Washington, D.C.: Office of Water Regulations and Standards, Criteria and Standards Division, USEPA.

U.S. Environmental Protection Agency (USEPA). 1980b. An exposure and risk assessment for dichloroethanes. Final draft report.

U.S. Environmental Protection Agency (USEPA). 1984. Health effects assessment for 1,1-dichloroethane. ECAO-CIN-H027 (Final Draft). Cincinnati, OH: Environmental Criteria and Assessment Office. September.

U.S. Environmental Protection Agency (USEPA). 1986a. Superfund public health evaluation manual. EPA 540/1-86/060. Washington, D.C.: Office of Emergency and Remedial Manual.

U.S. Environmental Protection Agency (USEPA). 1986b. Quality criteria for water, 1986 ("The Gold Book"). EPA 440/5-86-0001. Washington, D.C.: Office of Water Regulations and Standards.

U.S. Environmental Protection Agency (USEPA). 1989. Health effects assessment summary table. Washington, D.C.: Office of Health and Environmental Assessment. April.

Valvani, S.C., S.H. Yalkowsky, and T.J. Roseman. 1980. Solubility and partitioning. IV. Aqueous solubility and octanol-water partition coefficients of liquid nonelectrolytes. J. Pharm. Sci. 70 (5):502-202.

Verschueren, K. 1977. Handbook of environmental data on organic chemicals. New York: Van Nostrand Reinhold Co.

Weast, R.E., ed. 1981. Handbook of chemistry and physics. 62nd ed. Cleveland, OH: CRC Press.

DICYCLOPENTADIENE[1]

Summary

No data on the toxicity of dicyclopentadiene (DCPD) to humans were located in available literature. DCPD was not mutagenic in standard microbial assays (both activated and inactivated). No evidence of toxicity was observed following subchronic dietary administration to rats, mice or dogs at levels ranging up to 750, 273, or 1,000 ppm, respectively. No reproductive effects occurred following DCPD exposure in male and female rats, nor were doses of DCPD teratogenic when administered to pregnant rats during gestation days 6-15. Subchronic (90 day) inhalation exposure of male rats at 1 ppm and rats and mice at 5.1 and 51 ppm resulted in signs of kidney toxicity that subsided or decreased in severity upon termination of exposure.

CAS Number: 77-73-6

Chemical Formula: $C_{10}H_{12}$

IUPAC Name: Dicyclopentadiene

Important Synonyms and Trade Names: DCPD

Chemical and Physical Properties:

Molecular Weight: 132.21

Odor and appearance at room temperature: waxy solid; irritating, unpleasant odor.

Melting Point:	32.9°C	(Rosenblatt et al., 1975)
Boiling Point:	170°C	(Cogley and Foy, 1978)
Solubility in Water:	20 mg/l	(estimated: Lyman et al., 1982)

[1] Modified from the toxicity profile in the On-Post Exposure Assessment, which was compiled from: United States Army Medical Bioengineering Research and Development Laboratory (USAMBRDL), 1985. Physical, Chemical, and Toxicological Data Summaries for 62 Compounds Present at Rocky Mountain Arsenal. USAMBRDL. Fort Detrick, Frederick, MD.

Log Octanol/Water Partition Coefficient (K_{ow}): 3.14 (Lyman et al., 1982) Fragment Method

Soil/Water Partition Coefficient (K_{oc}):

1,217	Lyman et al. (1982) Eqn 4-8 (log K_{ow} = 3.14)
806	Lyman and Loreti (1987) (log K_{ow} = 3.14)

Bioconcentration Factor:

53	Bentley et al. (1976) (experimental)
114	Davies and Dobbs (1987) Eqn. A (S = 20)
143	Lyman et al. (1982) Eqn. 5-2 (log K_{ow} = 3.14)
115	Davies and Dobbs (1987) Eqn B (log K_{ow} = 3.14)
53.9	Davies and Dobbs (1984) Eqn C (log K_{ow} = 3.14)

Specific Gravity: 0.98 (Rosenblatt et al., 1982)

Vapor Pressure: 2.2 mm Hg at 25° C (estimated; Rosenblatt et al., 1975)
1.4 mm Hg at 20° C (estimated; Rosenblatt et al., 1975)

Henry's Law Constant: 1.9×10^{-2} atm-m^3/mole (calculated)
8.28×10^{-1} Dimensionless
1.2×10^{-2} atm-m^3/mole (calculated)

Transport and Fate

The relatively high vapor pressure of DCPD indicates the importance of volatilization (evaporation) as a transport process from surface water to the atmosphere. The chemical fate of DCPD in the atmosphere is not definitively known; however, photodegradation may occur. DCPD is virtually insoluble in water (Cogley and Foy, 1978). A range of estimated soil-water partition coefficients (K_{oc}) is reported above and indicates that sorption of DCPD to soils will occur. The combined low water solubility and high organic partition coefficients suggest that dicyclopentadiene will not be mobile in the environment. The half-life of DCPD in soil ranges from six months to one year depending on ambient conditions (Cogley and Foy, 1978). Degradation to more stable forms (degradation forms were not reported) occurs and the reported half-lives of these products range from one year to greater than five years (Cogley and Foy, 1978). Spanggord et al. (1979) reported an estimated half-life of 4-7 years for DCPD incubated (25°C) soil samples.

Biodegradation in aquatic systems is not likely to be extensive (Spanggord et al., 1979). An estimated 76 day or greater half-life of DCPD in water samples was also reported by Spanggord et al. (1979), based upon sunlight exposure (photolysis) tests. A 5.3 day half-life for DCPD in water samples (25°C, without recharge) was also observed. Uptake of less than 100 ppm DCPD was observed in plants which were grown in hydroponic solutions (1,000 ppm) (O'Donovan and Woodward, 1977). Evidence of stunted growth was also seen in plants at this concentration.

A range of experimental and estimated bioconcentration factors (BCFs) for dicyclopentadiene is also reported above. ASTM (1985) indicates that chemicals with bioconcentration factors less than approximately 100 have low potential for causing harm to wildlife and human health via biomagnification of residues up food chains. The magnitude of the concentration factors suggests that appreciable bioconcentration or biomagnification of DCPD residues is not likely to occur.

Health Effects

The toxicity (both acute and chronic) of DCPD has been assessed in a variety of mammalian and non-mammalian species. Clinical signs following acute exposure include decreased activity, ataxia, conic-tonic spasms, unsteady gait, and prostration followed by recovery or death. These signs plus the lipophilicity of DCPD are suggestive of effects on the central nervous system (CNS) (Palmer, 1979, and others). Necropsy findings after acute or short-term subchronic exposures may show no gross lesions (Kinkead, 1971) or congestive lesions in brain, liver, spleen, kidneys, or lungs (Kinkead, 1971; Palmer, 1979; Cysewski et al., 1971; and others).

No data on the toxicity of DCPD in humans were located in available literature. DCPD was not mutagenic in microbial assays in 5 strains of Salmonella typhimurium and in Saccharomyces cerevisiae, both with and without metabolic activation (Hart, 1980). No data on the carcinogenicity of DCPD were located. DCPD is thus categorized as an EPA Group D chemical (insufficient evidence to determine carcinogenicity).

Dicyclopentadiene was minimally irritating to rabbit skin and did not produce evidence of systemic toxicity following application (Hart, 1976, and Kinkead, et al., 1971). No signs of toxicity were produced by dermal application up to 2000 mg/kg (Hart, 1976) even though clinical signs are seen at oral doses an order of magnitude lower, indicating that dermal absorption is not very efficient. In the standard Draize protocol, DCPD was judged to produce moderate irritation of the conjunctiva, but no corneal damage or irritation, and all effects were reversible within 3 days (Hart, 1976).

No evidence of toxicity followed its dietary administration for 90 days to rats at levels up to 750 ppm or to mice at levels up to 273 ppm (Hart, 1976). Hart (1980) administered DCPD to beagle doges in their diets for 13 weeks at concentrations of 100, 300, or 1,000 ppm. Clinical pathological evaluations, including analyses of clinical chemical constituents of serum, urine, and hemograms were performed at monthly intervals. Tissues from control and treated dogs were compared histopathologically. No significant toxicity was observed with the possible exception of minor indications of intestinal distress expressed as vomiting and soft stool among treated groups, especially the highest dose (Hart, 1980). Signs of intestinal distress were also observed in the control animals. The No-Observed-Adverse-Effect-Level identified from this study was 1,000 ppm (25 mg/kg/day). No effects on fertility indices, live-to-total pup ratios, mean litter sizes, pup survival indices or mean body weights of pups post partum were observed in rats given 80 or 750 ppm DCPD in the diet prior to mating. Likewise, no dose-related teratogenic effects were observed in pregnant females administered 80, 250, or 750 ppm in the diet during days 6-15 of gestation (Hart, 1980). DCPD had oral LD_{50}s of 520 and 378 mg/kg in male and female rats and 190 and 250 mg/kg in male and female mice (Hart, 1976).

A 90-day inhalation study was conducted in F334 rats and $B6C3F_1$ mice. Dodd et al. (1982) (as reported in USEPA, 1987). In this study, rats (51 males and 51 females) and mice (45 males and 45 females) were exposed to 0, 1, 5.1 or 51 ppm (0, 5.4, 27.6, or 276 mg/cu.m) for 6 hours/day, 5 days/week. Groups of nine animals/sex were sacrificed

after 10, 30, and 64 inhalation exposures, and postexposure sacrifices were made at 29 and 92 days. Parameters of toxicity examined included clinical observations, body weight, organ weights (kidneys, liver, lung and testes), food and water consumption (rats only), urinalysis (rats only), serum chemistry, and hematological, ophthalmological and gross pathological evaluations. Histological evaluation of all rat kidney and urinary bladders was performed, and other selected tissues were examined for the high dose and control rats after 64 inhalation exposures. Several of these parameters were affected. Exposure related increases in relative and absolute kidney weight were observed in the 51 ppm males. Renal dysfunction, determined by urinalysis and urinary chemistry, occurred in the 5.1 and 51 ppm male rats. Additional dicyclopentadiene-related effects observed at 1 ppm or greater were tubular protein accumulation and epithelial cell casts. Most of these effects subsided or decreased in severity upon termination of exposure. Urine concentrating ability declined in the 51 ppm male rats during the post exposure period. The 5.1 ppm male rats were affected similarly but these effects were reversible. Kidney lesions such as severe tubular hyperplasia, tubular proteinosis and interstitial *nephritis at 5.1 ppm or greater were revealed by histological examination. Some of these* were attributable to the nephrotoxic effect of dicyclopentadiene and others to the normal aging process in these rats. The authors concluded that exposure to dicyclopentadiene at concentrations of 1 ppm or greater led to nephrotoxicity. A reversible increase in relative liver weight was also noted in the high-dose (51 ppm) male rats. An increase in body weight gain in female mice was noted at 51 ppm. In 51 ppm mice of both sexes, about 20% mortality attributable to pulmonary congestion (not confirmed by histological examination) with some case of renal failure was observed. Possible liver dysfunction was indicated by a slight increase in serum albumin in 5.1 and 51 ppm female mice. Increased relative and absolute liver weight was observed in the 5.1 ppm female mice; not other effects were observed in rats or mice.

In another inhalation study, Kinkead (1971) found increases in serum levels of liver enzymes in dogs exposed to DCPD at 23.5 and 32.4 ppm, 7 hours/day, 5 days/week for 89 exposures. Kidney lesions occurred in rats exposed to 35.2 and 73.8 ppm but not at

19.7 ppm for the same exposure duration as the dog study. However, at the 19.7 ppm exposure level, female rats had convulsions.

Toxicity to Wildlife and Domestic Animals

Dicyclopentadiene was found to be relatively non-toxic to mallard ducks (Aulerich et al, 1979). An oral LD_{50} could not be determined, even when levels administered were as high as 40,000 mg/kg. The oral LD_{50} in bobwhite quail was 1,010 mg/kg and greater than 1,000 mg/kg in mink. The biological half-life of DCPD residues in ducks and quail fed ^{14}C-DCPD treated diets averaged 12.7 hours and was not concentrated in adipose tissue of either species. The 96 hour LC_{50} for fathead minnows is 31.1 mg/l (Behtley et al., 1979).

Aulerich et al. (1979) maintained groups of mink on diets that provided dicyclopentadiene doses of 24, 42, 85, or 170 mg/kg/day for 12 months. This treatment period included one breeding season. The only effects were a significantly reduced testicular weight in the 170 mg/kg/day males and significantly decreased body weight of the offspring after 4 weeks of nursing at > 42 mg/kg/day.

Cysewski et al. (1981) report the effects of single doses of DCPD to 8 to 10 week old calves at 250, 500, 1000, or 2000 mg/kg body weight. Mild signs of intoxication, ataxia, and excess salivation were observed in calves given 250 mg/kg DCPD. At higher doses, these signs were intensified; in addition, calves fell and, while prostrate, exhibited running movements and tonic-clonic spasms. The severity of response was dose-related. All calves (the exact number is not available) given 2000 mg/kg and one calf given 1000 mg/kg died within 7 days of dosing. Clinical changes found were increased serum levels of creatine phosphokinase, SGOT (AST) and SGPT (ALT). The only consistent gross pathological change was congestion in a variety of tissues in calves given 2000 mg/kg.

Regulations and Standards

ACGIH Threshold Limit Value: TWA[2] = 30 mg/m^3 (5 ppm)

The value of 5 ppm was selected to prevent significant irritation and possible chronic effects from dicyclopentadiene. The value was chosen based on the rat NOEL of 12.7 ppm (Kinkead, et al., 1971) and on tests to determine the odor threshold of DCPD in which mild eye and throat irritation occurred in 7 minutes at 1 ppm and olfactory fatigue occurred in 24 minutes, but no fatigue occurred during a 30-minute exposure at 5.5 ppm. (ACGIH, 1986; no source reference provided). ACGIH (1986) reports that the odor of DCPD is detectable below 0.2 ppm but does not become noticeably irritating below 10 ppm. The levels reported at which irritation occurs (1 ppm and 10 ppm) appear to be in conflict.

D_T Value

The D_T value is defined as that contaminant intake rate (mg/kg/day) that should not induce an adverse effect to human health or should not pose a risk of cancer occurrence greater than a predetermined risk level.

For dicyclopentadiene (DCPD), the oral D_T value is based on a subchronic oral toxicity study utilizing dogs (Hart, 1980). No toxicity was observed (histopathologically or otherwise) at any dose level, with the exception of some vomiting and soft stools. The identified No-Observed-Adverse-Effect-Level from this study was 1,000 ppm (25 mg/kg/day). Since no significant toxic effects were observed, the true highest NOEL is probably higher than this level, making protective values derived from this level conservative. An Uncertainty Factor (UF) of 1,000 is employed to address the extrapolation of results to humans (10), intraspecies variability (sensitive subgroups) (10), and to address the use of a subchronic rather than a chronic study (10). Derivation of the oral D_T for dicyclopentadiene is as follows:

[2] Time weighted average

$$\text{Oral } D_T = \frac{\text{NOEL}}{\text{UF}}$$

$$= \frac{25 \text{ mg/kg/day}}{1{,}000}$$

$$= 0.025 \text{ mg/kg/day}$$

USEPA (1987) and USEPA (1989) report a slightly different chronic RfD of 0.032 mg/kg/day. This value is based on the NOEL of 32 mg/kg/day in rats administered DCPD in the diet at 690 ppm for three generations (Litton Bionetics, 1980, as reported in USEPA, 1987). Again, no effects were observed at any level in the study, making this value conservative. An uncertainty factor of 1,000 was applied.

A different inhalation D_T is calculated by the EPA based on the Dodd et al. (1982) study (as reported in USEPA, 1987 and USEPA, 1989)[3]. In this study, rats and mice were exposed to 0, 1, 5.1 or 51 ppm (0, 5.4, 27.6, or 276 mg/cu.m) for 6 hours/day, 5 days/week. Exposure at *concentrations* >1 *ppm* [greater than or equal to] (equivalent to an "expanded" dose of 0.61 mg/kg/day) resulted in nephrotoxicity, which was manifested by structural and functional alterations. The expanded dose is the dose delivered in an experiment adjusted to be equivalent to the dose that would be delivered over the expected environmental exposure. In this case, the expanded exposure level for 5.4 ppm is calculated to be 0.96 mg/cu.m. by multiplying 5.4 ppm by 6/24 hours per day and 5/7 days per week, and the expanded dose is figured by multiplying that exposure level by the reference rat inhalation rate of 0.223 cu.m./day and dividing by the reference rat body weight of 0.35 kg. The EPA then calculates a subchronic reference dose (RfD) of 6E-04 mg/kg/day using an uncertainty factor of 1000 (10 for

[3] Apparently, there is an editorial error in USEPA (1987) that is perpetuated in USEPA (1989). In the risk assessment section but not in the summary of subchronic effects section of USEPA (1987), mention is made of liver toxicity; USEPA (1989) lists liver toxicity at 1 ppm as the effect of concern on which the RfD is based. The original report (Dodd, 1982) states that only kidney effects were significant.

interspecies extrapolation, 10 to protect sensitive individuals, and 10 for the use of a LOAEL) and a chronic RfD of 6E-05 mg/kg/day using an uncertainty factor of 10,000 (1000 as above, plus 10 for the use of a subchronic study to predict a chronic RfD) (USEPA, 1987). The D_T value is equivalent to the chronic RfD.

It should be noted that this study (Dodd, 1982) reported a LOEL that is lower than other inhalation studies report. Kinkead (1971) found increases in serum levels of liver enzymes in dogs exposed to DCPD at 23.5 and 32.4 ppm, 7 hours/day, 5 days/week for 89 exposures. In the Kinkead study, kidney lesions occurred in rats exposed to 35.2 and 73.8 ppm but not at 19.7 ppm for the same exposure duration as the dog study. The response observed at the 1 ppm exposure level in the Dodd study was species, sex and route specific; it was only observed in the male rat kidney following inhalation exposure, although 90 day feeding and inhalation studies have been conducted in rats, mice, and dogs. Only proteinosis was observed at that exposure level, and it may not be dose related. For example, at week 17 of the study, control levels of proteinosis were higher than the medium and low dose group levels. Other renal effects were observed at the 5 and 51 ppm exposure levels. If the proteinosis is not an "adverse" effect, then 1 ppm would be a NOAEL, and a UF of 1000 would be applied; the D_T would then be 6E-04 mg/kg/day.

A third calculation of the RfD (and D_T) may be made based on the observation that the male rat kidney response to hydrocarbons is typically more sensitive than that of female rats or of other rodents, and it typically overestimates the human response to hydrocarbons. The uncertainty factor of 10 for conservative extrapolation from one species to another is not necessary when the experimental animal response is already more sensitive than the human response. Considering the mildness of the effects in all animals at the 1 and 5.1 ppm levels, a total uncertainty factor of 100 (10 for sensitive subgroups, 10 for subchronic to chronic extrapolation) may be applied to the 1 ppm level to derive an RfD (and D_T) of 6E-03 mg/kg/day.

These considerations provide a range of potential inhalation RfDs (and D_Ts) of from 6E-05 to 6E-03 mg/kg/day. The true conservative and protective dose probably lies within that range.

REFERENCES

ASTM. 1985. Standard Practice for Conducting Bioconcentration TEsts with Fishes and Saltwater Bivalve Mollusca. Designation E 1022-84, pages 590-62. In: 1985 Annual Book of ASTM Standards, Volume 11.04. American Society for Testing and Materials, Philadelphia, PA.

AULERICH, R.J., T.H. COLEMAN, D. POLIN, R.K. RINGER, K.S. HOWELL, R.E. JONES, AND T.J. KAVANAGH. 1979. Toxicology Study of Diisopropyl Methylphosphonate and Dicyclopentadiene in Mallard Ducks, Bobwhite Quail and Mink. Final Report. Contract No. DAMD 17-76-C-6054. Michigan State University, Poultry Science Department.

BENTLEY, R.E., G.E. LE BLANC, T.A. HOLLISTER, AND B.H. SLEIGHT III. 1976. Acute Toxicity of Diisopropyl Methylphosphonate and Dicyclopentadiene to Aquatic Organisms. Contract No. DAMD 17-75-C-5073. EG and G Bionomics, Inc., Wareham, MA. NTIS No. AD AO27750.

COGLEY, D.R. AND W. FOY. 1978. Readily Available Data on 169 Compounds Associated with Operations at Rocky Mountain and Pine Bluff Arsenals. United States Army Medical Research and Development Command, Ft. Detrick, Frederick, MD December 1978. AD AO74214.

CYSEWSKI, S.J., J.S. PALMER, H.R. CROOKSHANK, AND E.G. STEEL. Toxicologic evaluation of diisopropyl methylphosphonate and dicyclopentadiene in cattle. Arch. Environ. Contam. Toxicol 10(5):605-15.

DODD, D.E., L.C. LONGO, AND D.L. EISLER. 1982. Dicyclopentadiene vapor ninety-day inhalation study on rats and mice. Bushy Run Research Center,

Export, PA. TSCA 83 submission by Exxon Chem. Amer. Doc. I.D. 88-8300464, Odd Doc. I.D. 8EHQ-0283-0364. Microfiche No. OTS 204864.

DAVIES, R.P., AND A.J. DOBBS. 1984. The Prediction of Bioconcentration in Fish. Water Res. 18(10):1253-1262.

HART, E>R> 1976. Mammalian Toxicological Evaluation of DIMP and DCPD (Phase 2), Final Report. Contract No. DAMD 17-77-C-7003. Litton Bionetics, Inc., Kensington, MD

KINKEAD, E.R., U.C. POSSANI, D.L. GEARY, AND C.P. CARPENTER. 1971. The Mammalian Toxicity of Dicyclopentadiene. Toxicology and Applied Pharmacology 20:552-561.

LYMAN, W.J., AND C.P. LORETI. 1987. Prediction of Soil and Sediment Sorption for Organic Compounds. Final Report. U.S. Environmental Protection Agency, Monitoring and Data Support Division, Office of Water Regulations and Standards. Washington, D.C.

O'DONOVAN, P.A., AND J.E. WOODWARD. 1977. Investigation of the Soil Translocation and Phytotoxicity of DIMP and DCPD. Final Report, Contract No. DAMD 17-75-C-5069. Aerojet Ordinance and Manufacturing Co., Downey, CA. NTIS No. AD AO58790.

PALMER, J.S., CYSEWKSI, S.J., CROOKSHANK, H.R., STEEL, E.G., AND IVIE, G.W. 1979. Toxicological Evaluation and Fate of Diisopropyl methylphosphonate (DIMP) and Dicyclopentadiene DCPD) in Cattle. Project 7609, U.S. Army Medical Research and Development Command (from Rocky Mountain Arsenal Information Center, Commerce City, Colorado).

ROSENBLATT, D.H., T.A. MILLER, J.C. DACRE, I. MUUL AND D.R. COGLEY. 1975. Problem definition studies on potential environmental pollutants. II. Physical, Chemical, Toxicological, and Biological Properties of 16 substances. Technical Report 7509. U.S. Army Medical Bioengineering Research and Development Laboratory, Fort Detrick, Frederick, MD.

SPANGGORD, R.J., T.W. CHOU, AND W.R. MABEY. 1979. Studies of Environmental Fates of DIMP and DCPD. Final Report. Contract DAMD 17-78-C-8053, DTIC AD No. AO78236. SRI International, Menlo Park, CA.

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). 1985. Toxicology Handbook. Principles Related to Hazardous Waste Site Investigation. ICAIR, Life Systems, Inc. Contract No. TES EMI-LS.

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). 1987. Health and Environmental Effects Document for cyclopentadiene and dicyclopentadiene. OSWER. ECAO-CIN-GO12, September, 1987. Final Draft.

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). 1989. Health Effects Assessment Summary Tables. Second Quarter, FY 1989. OERR 9200.6-303-(89-2).

ENDRIN

Summary

Endrin, a stereoisomer of dieldrin, is an insecticide, rodenticide and avicide belonging to the chemical class of cyclodienes. It is retained in soils and sediments and is very persistent in the environment by virtue of its structure and physical/chemical properties. It is readily bioaccumulated by aquatic organisms. Humans and rats appear to metabolize and excrete endrin fairly rapidly from blood (the half life ranges from one to several days). Endrin is acutely toxic to mammals, aquatic organisms, and terrestrial wildlife. Its toxic effects are similar to those of dieldrin: acute toxic effects include muscle tremors, hypersensitivity to stimuli, convulsions and death, while chronic effects in experimental animals include nervous system damage as shown by hypersensitivity and occasional convulsions, body weight depression, and damage to the liver and kidneys. It was not mutagenic in several tests. Endrin is currently classified by the EPA as "D" (not classifiable as to carcinogenicity), although as recently as 1987 it was classified as an "E" chemical (no evidence of carcinogenicity for humans) based on negative results in 4 bioassays (EPA, 1987b). Some tests for developmental effects resulted in maternal toxicity but no teratogenicity; others, at doses up to half the LD_{50} showed reproductive and developmental effects along with maternal toxicity.

CAS Number: 72-20-8

Chemical Formula: $C_{12}H_8Cl_6O$

IUPAC Name: 1,2,3,4,10-Hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a octahydro-endo-1,4:5,8-dimethanonaphthalene

Important Synonyms and Trade Names: Endrin, hexadrin, mendrin

Chemical and Physical Properties

Molecular Weight: 380.9

Melting Point: 200°C

Decomposes: 235°C

Specific Gravity: 1.65 at 25°C

Solubility in Water: 0.25 mg/liter at 25°C
0.23 mg/liter at 25°C
(Rosenblatt et al. 1975)
0.1 mg/liter (Rao and Davidson 1983)
0.024 mg/liter (Kenaga 1980)

Solubility in Organics: Soluble in acetone, benzene, carbon tetrachloride, hexane, and xylene; insoluble in methanol.

Log Octanol/Water
Partition Coefficient (K_{ow}): 5.34 (Kenaga 1980)

3.21 (Rao and Davidson 1983)

4.44 (Kadeg et al. 1986)

Soil/Water Partition Coefficients (K_{oc}):

1,312; 26,510	Lyman et al. (1982) Eqn 4-8 (log K_{ow} = 3.20; 5.60)
34,000	Kenaga (1980)
897; 66,440	Lyman and Loreti (1987) (log K_{ow} = 3.20; 5.60)
1,249; 5,640	Kadeg et al. (1986) (log K_{ow} = 3.20; 5.60)
3,630	Kadeg et al. (1986), (geometric mean of 2 literature values)

Bioconcentration Factor:

4,050	Kenaga (1980) (experimental)
1,360	Kenaga (1980) (experimental)
2,377	Davies and Dobbs (1984) Eqn B (log K_{ow} = 5.34)
1,415.7	Davies and Dobbs (1984) Eqn A (S = 0.23)
5,012	Davies and Dobbs (experimental)
6,736	Lyman et al. (1982) Eqn 5-2 (log K_{ow} = 5.34)
1,043	Davies and Dobbs (1984) Eqn 5-2 (log K_{ow} = 5.34)
250	Davies and Dobbs (1984) Eqn C (log K_{ow} = 4.44)
690	Davies and Dobbs (1984) Eqn B (log K_{ow} = 4.44)
1,390	Lyman et al. (1982) Eqn 5-2 (log K_{ow} = 4.44)
1,640	Argyle (1973) (experimental)

13,000 Hermanutz (1987) (experimental)

Vapor Pressure: 2.7×10^{-7} mm Hg at 25°C (Rao and Davidson 1983)
2.0×10^{-7} mm Hg at 25°C (Rosenblatt et al.1975)

Henry's Law Constant: 4.4×10^{-7} atm-m^3/mole (calculated)
1.8×10^{-5} Dimensionless
4.2×10^{-6} atm-m^3/mole (calculated)
1.8×10^{-4} Dimensionless

Transport and Fate

Endrin is quite persistent in the environment. Volatilization from soil surfaces and from surface water is not likely to be an important transport process (Nash 1983) in light of its very low vapor pressure. For the small portion that may volatilize, photolysis to delta-keto endrin and endrin aldehyde are important chemical fate processes.

A range of estimated soil-water partition coefficients (K_{oc}) is reported above and indicates that sorption of endrin to soils/sediments and dissolved organic materials will occur. Pavlou (1980) estimates that sorption of organochlorine pesticides such as endrin is very high. The combined low water solubility and high organic partitioning of endrin indicates that little environmental mobility will occur. Rosenblatt et al. (1975) report less than 10 cm of movement in situ following 150 cm of rainfall. Microbial degradation by soil microorganisms occurs but appears to be limited (Rosenblatt et al. 1975). The extent of utilization and the decomposition products were not reported. The half-life of endrin in soil varies from one day to 12 years, depending on conditions such as soil properties, agricultural processes, topology, and weather conditions (EPA, 1987b).

Uptake in plants varies with species. For example, root crops (potatoes) grown in treated soil exhibited levels about twice that of the soil in which they were grown

(Telekar et al. 1983). Levels in pasture crops appear to be less than those in soil (Chawla et al. 1981). Endrin is not considered phytotoxic (National Library of Medicine, 1989.)

A range of experimental and estimated bioconcentration factors (BCFs) for endrin is also reported above. ASTM (1985) indicates that chemicals with bioconcentration factors less than approximately 100 have low potential for causing harm to wildlife and human health via biomagnification of residues up food chains. The magnitude of the concentration factors suggests that bioconcentration and potential biomagnification will occur. Tissue levels of endrin have been observed in both plants and animals; the levels are usually low. Although a weighted average BCF for aquatic organisms of importance in the human food chain is calculated by the EPA to be 3,970, bioaccumulation is usually short-lived, and tissue burdens diminish rapidly once the environmental source is removed (EPA, 1980).

Pharmacokinetics

Endrin is absorbed by the skin, lungs and the gut, but the rates have not been well documented. Mammals do not store endrin in significant quantities. No residues were detected in plasma, adipose tissue, or urine of workers occupationally exposed to endrin (Hayes and Curley, 1968, as cited in EPA, 1980). Endrin is probably metabolized in the liver. Metabolites are excreted in the urine and feces. Little is known about the persistence and toxicity of endrin metabolites. Some metabolites, such as 12-ketoendrin and syn-12-hydroxyendrin, may be more toxic and persistent than the parent compound (EPA, 1980 and EPA, 1987a).

Health Effects

Acute toxicity

The acute toxicity of endrin is due to its effects on the central nervous system. The acute oral LD_{50} has been given as 3 mg/kg in the rat and 1.37 mg/kg in the mouse (Sax 1979). Treon and Cleveland (1955) found LD_{50}s ranging from 7 to 43 mg/kg in

rats, depending on age and sex. Acute oral LD_{50} values for several mammalian species range from 1.37 in the mouse (USEPA, 1980) to possibly as high as 50 mg/kg in the goat (Hudson, 1984). Treon and Cleveland (1955) found a dermal minimum lethal dose for rabbits to be 60 to 94 mg/kg. Acute toxic effects observed in experimental animals include nervous system signs such as tonic-clonic muscle contractions, muscle tremors, salivation, seizures, hyperexcitability, convulsions alternating with severe central nervous system depression, and death.

Outbreaks of human poisoning have resulted from accidental contamination of foods; a dose that may cause convulsions in humans has been estimated at 0.2 mg/kg from these incidents. Symptoms of acute poisoning include convulsions, vomiting, abdominal pain, nausea, dizziness, and headache. Respiratory failure is the most common cause of death from endrin poisoning (USEPA 1980).

Chronic toxicity

Chronic exposure to low levels of endrin results primarily in nervous system damage; however, adverse effects to the heart, lungs, liver, and kidneys also occur. A two-year study in dogs (Velsicol Chemical Corporation, 1969, in USEPA, 1989) showed that dogs receiving 2 or 4 ppm endrin in the diet experienced occasional convulsions, slightly increased relative liver weights, and mild histopathological effects in the liver (slight vacuolization of hepatic cells). No adverse effects on these parameters or on growth, food consumption, behavior, serum chemistry, urine chemistry or histological appearance of major organs occurred at 1 ppm or less. Treon et al. (1955) fed diets containing 1 to 100 ppm endrin to Carworth rats for 2 years. Rats receiving 50 or 100 ppm showed hypersensitivity to external stimuli, occasional convulsions, liver degeneration, and (after 80 weeks) increased mortality in males and females; males receiving 25 ppm also showed increased mortality. Males at 5 and 25 ppm had increased relative liver weights compared with controls. Treon et al (1955) also fed endrin to dogs for 18 months and found increased kidney and heart weights in the 3 and 4 ppm dose groups.

Chronic exposure in workers has been monitored (Jager, 1970). The threshold level of endrin in the blood below which no signs of intoxication were seen was 0.050-0.100 ug/ml. Surveillance of 233 workers with 4 to 13 years' exposure showed no abnormalities other than those that would be expected in any similar group (EPA, 1987a).

Mutagenicity

Endrin has not been shown to be mutagenic in microbial systems with or without activation (50 Federal Register 47011). Endrin was tested for mutagenicity in the Salmonella/microsome preincubation assay using a protocol approved by the National Toxicology Program. Endrin was tested over a wide range of doses (0, 100, 333, 1000, 3333, and 10,000 ug/plate) in four Salmonella typhimurium strains (TA98, TA100, TA1535, and TA1537) in the presence and absence of Aroclor-induced rat or hamster liver S9. These tests were negative. The highest ineffective dose level tested (not causing the formation of a precipitate) in any Salmonella tester strain was 333 ug/plate (Zeiger, 1987). Endrin did not cause unscheduled DNA synthesis in primary rat or hamster hepatocytes, and sister chromatid exchange frequencies were not significantly elevated in activated and non-activated human lymphoid cells. Genotoxicity thus does not appear to be an area of concern (EPA, 1989).

Carcinogenicity

Endrin has not been shown to be carcinogenic in several animal studies including the National Cancer Institute bioassay (50 Federal Register 47011, Wed. Nov. 13, 1985). The potential carcinogenic effects of endrin have been evaluated following oral exposure to 1-100 ppm endrin in the diet of Carworth Farm rats, (Treon et al., 1955), Osborne-Mendel rats (Deichmann et al, 1970; NCI, 1979), C57Bl/6J mice (Witherup et al., 1970), C3D2F1/J mice (Witherup et al., 1970) and B6C3F1 mice (NCI, 1979). All of these studies are considered negative. Treon et al. (1955) also failed to note any increase in tumorigenesis in dogs exposed up to 18.7 months at the maximum

tolerated dose. The length of this study was insufficient to provide for the expected latency period in dogs.

The NCI (1979) bioassay was done in Osborne-Mendel rats (50/sex/group) and B6C3F1 mice (50/sex/group); matched control groups included 10 animals/sex/species. Since the number of animals in the matched control groups was small, pooled-control groups from concurrent pesticide bioassays were used for statistical evaluation. Endrin was administered daily in the diet for 80 weeks. Rats were observed for an additional 31 to 34 weeks and mice were observed for an additional 11 weeks. The initial doses for male rats and all mice were 2.5 or 5 ppm and for female rats were 5 or 10 ppm. Because of subsequent toxic effects, the doses for the female rats and male mice were reduced during the course of the studies. High-dose male mice were fed treatment and control diets on alternate weeks for 10 weeks. The resulting time-weighted average dose fed in the diets of treated animals was reported as follows: 2.5 or 5 ppm for male rats, 3 or 6 ppm for female rats, 1.6 or 3.2 ppm for male mice, and 2.5 or 5 ppm for female mice. When compared with pooled controls, a statistically significant increase in hemangioma was observed in low-dose male rats (0/49, 5/46, 3/47), and a significant increase in adrenal adenoma or carcinoma was seen in high-dose male rats (2/44, 4/46, 8/44). Islet-cell carcinoma incidence in male rats showed a significant positive trend but the pairwise comparisons were not significant. A statistically significant increase in pituitary adenoma was observed in the high-dose female rats (4/44, 11/47, 13/45) and a significant increase in adrenal adenoma or carcinoma was observed in the low-dose female rats (4/46, 14/49, 7/47) (EPA, 1989).

Ditraglia et al. (1981) conducted a retrospective cohort
study to examine the mortality of workers employed in the manufacture of organochlorine pesticides including endrin. No statistically significant excesses or deficits in mortality for any specific cancer site were noted. Limited follow-up time

(12 years), lack of exposure data, and few deaths give this study low power (EPA, 1989).

Endrin had been classified according to EPA's Carcinogenic Risk Assessment Guidelines in EPA's Group E (no evidence of carcinogenicity for humans) based on these negative results (USEPA 1987a, 1987b, and elsewhere). However, USEPA (1989) now gives endrin a classification of "D" (not classifiable as to carcinogenicity for humans) and states that "The inadequacies of several of the bioassays call into question the strength of the reported negative findings."

Reproductive and developmental effects

Some evidence exists for developmental toxicity of endrin (USEPA 1989), and no information has been found on any direct effects of endrin on the reproductive process. Teratogenic effects have not been observed in rats, and effects in mice and Syrian hamsters have only been observed to occur at dose levels much greater than those associated with chronic toxicity. Chernoff and Kavlock (1982) reported that 2 mg/kg/day administered orally to CD-1 mice on days 8 to 12 of gestation resulted in substantially reduced maternal body weights and a statistically significant 6% reduction in body weights of the pups on day 1, but no pup body weight difference remained by day 3. Kavlock et al. (1981) reported that adverse fetal effects occurred in CD-1 mice treated on days 7 to 17 of gestation with 1 mg/kg/day, but maternal toxicity occurred at a lower dose (0.5 mg/kg/day) as well; they also found that endrin markedly reduced maternal weight in rats dosed on days 7 to 20 at doses above 0.15 mg/kg/day but endrin produced no apparent effects on the fetus even at the highest dose tested (0.45 mg/kg/day). Gray et al. (1981) exposed rats to endrin at 0.15 or 0.30 mg/kg/day and found they were 30% more active than controls prior to weaning, but not after. A study (Ottolenghi, 1974) in Golden Syrian hamsters gavaged on day 7, 8, or 9 of gestation with 5 mg/kg/day produced fetal death, growth retardation, and congenital abnormalities in 28% of fetuses treated on day 8; abnormalities included open eye, webbed feet, cleft palate, and fused ribs. The dose administered was half

of the oral LD_{50} for hamsters. Another study in hamsters (Chernoff et al, 1979) in which animals were gavaged on days 5 to 14 of gestation resulted in maternal lethality at doses of 1.5 mg/kg/day and above; fetal toxicity, including increased mortality, meningoencephales, reduced fetal weight and reduced skeletal ossification) occurred at doses above 0.75 mg/kg/day. Whether any of these fetal effects would occur at exposure levels that are below those that would also produce maternal toxicity is an important question.

Toxicity to Wildlife and Domestic Animals

Endrin is very toxic to aquatic organisms. Fresh water fish were generally more sensitive than invertebrates, with species mean acute values ranging from 0.15 to 2.1 ug/liter (USEPA 1980). LC_{50} values for saltwater organisms ranged from 0.037 to 14.25 ug/liter. Final acute values for freshwater and saltwater species were 0.18 ug/liter and 0.037 ug/liter, respectively (USEPA 1980). An acute-chronic ratio of 4.0 was determined from chronic tests on freshwater and saltwater species. Therefore, the freshwater final chronic value was calculated to be 0.045 ug/liter and the saltwater final chronic value was determined to be 0.0093 ug/liter (USEPA 1980).

Endrin is acutely toxic to terrestrial wildlife and domestic animals and has been used as a rodenticide and an avicide. It can also cause central nervous system effects and reproductive disorders following chronic exposure. Other effects observed in animals exposed to endrin include abnormal behavior, increased postnatal mortality, and increased fetal death. The LD_{50} values for a variety of birds are 5.64 mg/kg (mallard), 1.1 mg/kg (grouse), 1.2 mg/kg (quail) and 1.8 mg/kg (pheasant). Hudson et al. (1984) estimates that the LD_{50}s for mule deer and domestic goat are within the ranges of 6.25-12.5 mg/kg and 25-50 mg/kg, respectively, based on tests with 3 deer and 2 goats.

As in the case of mammals, reproductive and developmental studies in wild avian species have given mixed results. The National Academy of Sciences (1977) reported

that quail fed 1 ppm in the diet produced no eggs during the reproductive period, and that endrin fed at 10 ppm reduced egg production in pheasants and reduced survival of the chicks. In a different study, concentrations of 0, 1, and 3 ppm endrin in dry duck mash were fed to mallards (Anas platyrhynchos) starting in December. Health and reproduction were measured the following spring and summer. One male fed 3 ppm died with a diagnostically lethal level of 2.0 ppm (wet wt) in its brain. Birds fed 1 ppm reproduced as well as, if not better than, controls. Birds fed 1 ppm had significantly greater hatching success of fertile eggs than did those fed 0 or 3 ppm, and their clutches hatched significantly earlier than did those of birds fed 3 ppm. Mallards fed 3 ppm appeared to reproduce more poorly than controls, but this finding must be regarded with caution because the results of statistical tests often were not significant (Spann et al, 1986, cited in National Library of Medicine, 1989). Again, reproductive and developmental effects were seen at dose levels that apparently also produced parental toxicity.

Regulations and Standards

Aquatic Life (Freshwater)

Acute toxicity: 0.18 ug/liter
Chronic toxicity: 0.0023 ug/liter

Aquatic Life (Saltwater)

Acute toxicity: 0.037 ug/liter
Chronic toxicity: 0.0023 ug/liter

Human Health

Criterion: 1.0 ug/liter (water and fish ingestion)

Office of Drinking Water Health Advisories (USEPA 1987a):

One day HA: 0.02 mg/L (protective for a child)

Ten day HA: 0.005 mg/L (protective for a child)

Longer term HA: 0.016 mg/L (protective for an adult);
0.0045 mg/L (protective for a child)

Lifetime HA: 0.00032 mg/L

The one day HA was derived from the Revzin (1968) 7 day study in monkeys, with support from the Davies and Lewis (1956) report on human poisoning from contaminated bread. The ten day HA was derived from the Nelson et al. (1956) 13 week study in rats. The longer-term HA and the lifetime HA are both based on the 18 month study in dogs reported by Treon and Cleveland (1955); however, to derive the lifetime HA, an additional uncertainty factor of 10 and a source contribution factor of 20% were applied (USEPA 1987).

National Interim Primary Drinking Water Standard (USEPA):

0.002 mg/liter (MCL; 40 CFR 141.12 Subpart B)

OSHA PEL: TWA = 0.1 mg/m^3 (skin)

ACGIH TLV: TWA = 0.1 mg/m^3 (skin)

The ACGIH time-weighted average TLV is based on extrapolation from acute animal exposures and evidence that these levels do not appear to result in illness in man. It is also based on the oral LD_{50} in comparison with those of other pesticides of similar type (ACGIH, 1989). The skin notation indicates that toxicity may occur following adequate skin contact.

$\underline{D_T \text{ Value}}$

The D_T value is defined as that contaminant intake rate (mg/kg/day) that should not induce an adverse effect to human health or should not pose a risk of cancer occurrence greater than a predetermined risk level.

For endrin, the D_T value is based on the data used by EPA to establish the current reference dose (Rfd) (USEPA 1989). The study (Velsicol Chemical Corporation, 1969, in USEPA, 1989) assessed the toxicity of dietary endrin (0.1, 0.5, 1.0, 2.0, or 4.0 ppm) in dogs over a period of two years. The No-Observed-Effect-Level (NOEL) identified from the study is 1.0 ppm in the diet or 0.025 mg/kg/day. An Uncertainty Factor (UF) of 100 is employed to address extrapolation of the results to humans (10), and intraspecies variability (sensitive subgroups) (10). Derivation of the D_T for endrin is as follows:

$$D_T = \frac{\text{Noel (mg/kg/day)}}{\text{UF}}$$

$$= \frac{0.025}{100}$$

= 0.0003 mg/kg/day [Note: EPA has rounded off the number in deriving the RfD for endrin.]

REFERENCES

ACGIH. 1989. Documentation of the threshold limit values and biological exposure indices. Fifth Edition, 1986, with updates through 1989. Cincinnati: American Conference of Governmental and Industrial Hygienists.

ARGYLE, R.L. 1973. Endrin Uptake and Release by Fingerling Channel Catfish, Ictalurus punctatus. J. Fish. Res. Board Canada. 30:1743.

ASTM. 1985. Standard Practice for Conducting Bioconcentration Tests with Fishes and Saltwater Bivalve Mollusca. Designation E 1022-84, pages 590-62. In: 1985 Annual Book of ASTM Standards Volume 11.04. American Society for Testing and Materials, Philadelphia, Pennsylvania.

CHAWLA, R.P., K.L. KALRA, and B.S. JOIA. 1981. Absorption of Residues of Soil Applies Aldrin and Heptachlor in Potatoes. Judian J. Ent. 43(3):266-271.

CHERNOFF, N., R. J. KAVLOCK, and R. C. HANISCH. 1979. Perinatal toxicity of endrin in rodents. I. fetotoxic effects of prenatal exposure in hamsters. Toxicology 13:155-165.

DAVIES, R.P. and A.J. DOBBS. 1984. The Prediction of Bioconcentration in Fish. Water Res. 18(10):1253-1262.

GRAY, L.E. Jr., R. J. KAVLOCK, N. CHERNOFF, J. A. GRAY, AND J. MCLAMB. 1981. Perinatal toxicity of endrin in rodents. III. Alterations of behavioral ontogeny. Toxicology 21: 187-202.

HERMANUTZ, R.O. 1987. Endrin and Malathion Toxicity to Flagfish (Jordanella floridae). Arch. Environ. Contam. Toxicol. 1:159.

HUDSON, R.H., R.K. TUCKER, and M.A. HAEGALE. 1984. Handbook of Toxicity of Pesticides to Wildlife. Second Edition. United States Department of the Interior Fish and Wildlife Service. Resource Publication 153. Washington, D.C. 1984.

JAGER, K.W. 1970. Aldrin, Dieldrin, Endrin, and Telodrin. Elsevier Publishing Co., New York. 234 pages.

KADEG, R.D., S.P. PAVLOU, and A.S. DUXBURY. 1986. Elaboration of Sediment Normalization Theory for Non Polar Hydrophobic Organic Chemicals. U.S. Environmental Protection Agency, Criteria and Standards Division, Washington D.C.

KAVLOCK, R. J., N CHERNOFF, R. C. HANISCH, J. GRAY, E. ROGERS, AND L. E. GRAY, JR. 1981. Perinatal toxicity of endrin in rodents. II. Fetotoxic effects of prenatal exposure in rats and mice. Toxicology 21:141-150.

LYMAN W.J., and C.P. LORETI. 1987. Prediction of Soil and Sediment Sorption for Organic Compounds. Final Report. U.S. Environmental Protection Agency, Monitoring and Data Support Division, Office of Water Regulations and Standards. Washington D.C.

LYMAN, W.J., W.F. REEHL and D.H. ROSENBLATT. 1982. Handbook of Chemical Property Estimation Methods: Environmental Behavior of Organic Compounds. McGraw-Hill Book, Co., New York, NY.

NASH, R.G. 1983. Comparative Volatilization and Dissipation Rates of Several Pesticides from Soil. J. Agric. Food Chem. 31:310-317.

NATIONAL ACADEMY OF SCIENCES. 1977. Drinking water and health. Washington, D.C.: National Academy Press.

NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH (NIOSH). 1983. Registry of Toxic Effects of Chemical Substances. Data Base. Washington, D.C. October 1983.

NATIONAL LIBRARY OF MEDICINE. TOXNET. 1989. Hazardous Substances Data Bank. Endrin file. An on-line data base.

NELSON, S. C., T. L. BAHLER, W. V. HARTWELL, D. A. GREENWOOD, AND L. E. HARRIS. 1956. Serum alkaline phosphatase levels, weight changes, and mortality rates of rats fed endrin. J. Agric. Food Chem. 4: 696-700. Listed in USEPA (1987a).

OTTOLENGHI, A.D., J.K. HASEMAN AND F. SUGGS. 1974. Teratogenic effects of aldrin, dieldrin, and endrin in hamsters and mice. Teratology 9:11-16.

PAVLOU, S.P. 1980. Thermodynamic Aspects of Equilibrium Sorption of Persistent Organic Molecules at the Sediment-Seawater Interface: A Framework For Predicting Distributions in the Aquatic Environment. IN: Contaminants and Sediments. Volume 2. Baker, R.A. (Editor). Science Publishers, Inc. Ann Arbor, MI.

RAO, P.S.C. and J.M. DAVIDSON. 1983. Estimation of Pesticide Retention and Transformation Parameters Required in Nonpoint Source Pollution Models. In Overcash, M.R. and J.M. Davidson, editors. Environmental Impact of Nonpoint Source Pollution. Ann Arbor Science Publishers, Inc., Ann Arbor, MI.

REVZIN, A. M. 1968. Effects of chronic endrin administration on brain electrical activity in the squirrel monkey. Fed. Proc 27: 597. Listed in USEPA (1987a).

ROSENBLATT D.H., T.A. MILLER, J.C. DACRE, I. MUUL, and D.R. COGLEY. 1975. Problem Definition Studies on Potential Environmental Pollutants. II. Physical, chemical, Toxicological, and Biological Properties of 16 Substances. Technical Report 7509. U.S. Army Medical Bioengineering Research and Development Laboratory, Fort Detrick, Frederick, MD.

SAX, I.N. 1979. Dangerous Properties of Industrial Materials, Fifth Edition. Van Nostrand Reinhold Co., New York.

SPANN, J. W. et al, 1986. Environ Toxicol Chem 5(8): 755-9. Cited in National Library of Medicine, HSDB, 1989.

TELEKAR, N.S., J.S. CHEN, and H.T. KAO. 1983. Long-Term Persistence of Selected Insecticides in Subtropical Soil: Their Absorption by Crop Plants. J. Econ. Entomol. 76(2):207-214.

TREON, J.F. and F.P. CLEVELAND. 1955. Toxicity of Certain Chlorinated Hydrocarbon Insecticides for Laboratory Animals, with Special Reference to Aldrin and Dieldrin. J. Agric. Food Chem. 3:402-408.

TREON, J. G., F. P. CLEVELAND, AND J. CAPPEL. 1955. Toxicity of endrin for laboratory animals. J. Agric. Food Chem. 3:842-848.

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). 1979. Water-Related Environmental Fate of 129 Priority Pollutants. Washington D.D. December 1979. EPA 440/4-79-029.

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). 1980. Ambient Water Quality Criteria for Endrin. Office of Water Regulations and Standards, Criteria and Standards Division, Washington, D.C. October 1980. EPA 440/5-80-047.

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). 1986. Quality Criteria for Water, 1986 ("The Gold Book"). Office of Water Regulations and Standards, Washington, DC. EPA 440/5-86-001.

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). 1987a. Office of Drinking Water. Endrin Health Advisory.

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). 1987b. Health Effects Assessment for Endrin. Final Draft. Environmental Criteria and Assessment Office, Cincinnati, OH. ECAO-CIN-H089.

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA). 1989. Integrated Risk Information System (IRIS). Access Date: June, 1989. File on endrin, revised 10/01/89. [Note: This is a computerized data base.]

VERSCHUEREN, K. 1977. Handbook of Environmental Data on Organic chemicals. Van Nostrand Reinhold Co., New York.

WEAST, R.E., ed. 1981. Handbook of chemistry and Physics. 62nd ed. CRC Press, Cleveland, Ohio.

ZEIGER, E., et al. 1987. Environ Mutagen 9: 1-110, cited in National Library of Medicine. 1989. TOXNET Hazardous Substances Data Bank.